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THE INTRACRANIAL PRESSURE IN
HEALTH AND DISEASE

ASSOCIATION FOR RESEARCH IN
NERVOUS AND MENTAL DISEASE

A Series of Research Publications

VOLUMES PUBLISHED

- I. (1920) ACUTE EPIDEMIC ENCEPHALITIS
(Lethargic Encephalitis)
- II. (1921) MULTIPLE SCLEROSIS (Disseminated Sclerosis)
- III. (1923) HEREDITY IN NERVOUS AND MENTAL DISEASE
- IV. (1924) THE HUMAN CEREBROSPINAL FLUID
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- VI. (1926) THE CEREBELLUM
- VIII. (1927) THE INTRACRANIAL PRESSURE IN HEALTH AND
DISEASE

IN PREPARATION

- (1922) EPILEPSY AND THE CONVULSIVE STATE
(To be reconsidered in 1929, brought up to date
and published)
- (1928) THE VEGETATIVE NERVOUS SYSTEM

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ASSOCIATION FOR RESEARCH IN
NERVOUS AND MENTAL DISEASE

Vol. VIII of a Series of Research Publications

THE INTRACRANIAL PRESSURE IN HEALTH AND DISEASE

AN INVESTIGATION OF THE MOST RECENT
ADVANCES

The Proceedings of the Association
New York
December 28th and 29th, 1927

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With 181 illustrations and 33 tables

BALTIMORE
THE WILLIAMS & WILKINS COMPANY
1929

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COMPOSED AND PRINTED AT THE
WAVERLY PRESS
BALTIMORE, MD., U. S. A.

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PREFACE

THERE are many gaps in the knowledge of the normal and pathological variations in intracranial pressure, and of the effects upon the brain, the membranes, and the bones of the skull, of increase of pressure conditions within the cranial chamber.

These questions are intimately connected with the problems of symptomatology, diagnosis and the principles of treatment of hydrocephalus, of tumors of the brain, and of inflammatory and other conditions in which a rise in intracranial pressure is an important factor.

The sixth volume of the Proceedings of the Association for Research in Nervous and Mental Disease, on "The Cerebrospinal Fluid," has, logically, preceded this investigation of the various aspects of changes in intracranial pressure, and many facts with reference to the alterations in the cerebrospinal fluid, will be found in that volume.

While all aspects of the subject have not been considered, it is hoped that the research recorded in this volume will record the present status of knowledge of the intracranial pressure in health and disease.

Several investigations which had not been completed in time for the meeting of the Association, are included in this volume. The editors desire to express their appreciation to all contributors for the time and effort which has been devoted to the researches they have made, and to the many members of the Association who attended the meeting and added much to its success by their presence and their discussion.

C. A. E.

New York, October, 1928.

Section I

THE NATURE, MECHANICS AND GENERAL INVESTIGATION
OF INTRACRANIAL PRESSURE

CHAPTER I

THE RELATION OF VARIATIONS IN INTRAVENTRICULAR AND INTRACRANIAL PRESSURE TO HEADACHE¹

CHARLES A. ELSBERG, M.D.

THE presidential address at a medical society meeting, like the toastmaster's remarks at a formal dinner, should be short, for the audience has come to hear the chosen speakers and not the one who has been selected for the humble duty of presiding. What I have to say, therefore, shall occupy only a few minutes of your time.

The discovery of new facts in anatomy, physiology and pathology by means of experimental and clinical research is the foundation upon which the modern structure of scientific medicine has been erected, and the appreciation of that fact led a number of those whose interests lie in the fields of neurology and psychiatry to form this Association for Research.

As you well know, however, advance in science is a slow and laborious one and it is easy to wander from the trail that has, perhaps, already been blazed.

Efforts to prove facts eventually shown to be erroneous, and in that sense the errors themselves—often accepted as truth because of the scientific eminence of those who have promulgated them—have not only added to the sum of human knowledge but have acted as a powerful stimulus for further research.

The influence of Vesalius on anatomy was greater because of Galen and the Galenic doctrines. The discovery of the circulation of the blood, "the most momentous event in medical history since Galen's time," established a great scientific truth, but the opposition to Harvey's mechanical explanation of a vital phenomenon also had a far reaching influence upon the progress of medicine. The fantastic phrenology of Gall and Spurzheim was an effective stimulus which contributed to the wonderful development of the knowledge of the localization of functions in the cerebral cortex. The belief of

¹ Presidential Address delivered at the meeting of the Association for Research in Nervous and Mental Disease, New York, December, 1927.

Robert Koch that tuberculin was the cure-all for every lesion due to the tubercle bacillus was incorrect, but it led to enormous advances in our understanding of the nature and the principles of treatment of tuberculous disease. Paul Ehrlich, at first, believed in the efficacy of the 606th compound he had made as a "*therapia sterilisans magna*" for the specific organism of syphilis. He was in error, but the very error pointed the way to the rational treatment of that dread disease. And the modern studies of poliomyelitis and of encephalitis, although often leading to false conclusions, are building a mountain out of the molehill of our knowledge of these diseases.

What relation has all this, you may ask, to the ideals and the purposes of this Association? My primary object is to remind you that a research association has a double function to fulfill—not only that of the discovery of new facts, but also that equally difficult and often more laborious duty of disproving facts previously accepted as correct. The search must be for facts—facts well substantiated by the results of experiment and uninfluenced by flights of the imagination. "Put off your imagination as you take off your overcoat when you enter the laboratory," said Claude Bernard, "put it away from you during the experiment itself lest it hinder your observing power, but put it on again as you don your overcoat when you leave the laboratory." Needless to add, this sage advice of one who began his career as a poet and a dramatist, applies equally to laboratory and to clinical research.

Secondarily, I desire to present for your consideration a few facts concerning intracranial pressure and its relation to headache, and I hope that by the few introductory remarks already made, the ruts and cracks on the road that I am to traverse have been smoothed over by a judicious use of tar and oil, so that the passengers—my audience—will not be too much shaken up in spite of the fact that the vehicles' tires and mudguards may be covered by not a little useless material.

Many theories have been proposed for the explanation of the symptom "headache," which must be a disturbance of sympathetic or somatic nervous structures. Temporary obstruction of one or other foramen of Monro has been suggested, but such an obstruction has never been demonstrated excepting in intracranial expanding disease. Quincke considered that headache might be connected with variations in the amount of cerebrospinal fluid secreted by the chorioid plexuses—and there is some evidence to support such a theory. The ordinary

"headache" that occurs in many diseases, in disturbances of the gastrointestinal tract, in fever, and in states of increased intracranial pressure is usually described as due to distension or stretching of the dura with pressure of that membrane against the inner surface of the cranial bones. The very facts, however, that headache often occurs in states of diminished intracranial pressure, in anemia and in conditions in which the total blood volume and general blood pressure are diminished, throw some doubt upon such an explanation.

For many years, during the course of cranial operations performed under local anesthesia, I have investigated this subject, and I am convinced—as others have been—that excepting for the meningeal vessels, the dura is insensitive. The dura can be stretched and pulled upon, it can be distended to the maximum by the injection in all directions of fluid underneath it, without causing any pain or headache.

On the other hand, if intraventricular pressure is suddenly either lowered or raised by the removal of fluid or by the injection of fluid or air, typical headache is at once complained of. If one removes even as little as 5 to 10 cc. of fluid by means of suction or injects that amount of fluid or air rather quickly, the patient will almost regularly complain of a typical headache. In some instances in which the fluid was withdrawn from or injected into a frontal horn, the headache was located in the frontal region, and if the procedure was done in a posterior horn, the headache was occipital.

If, however, the injection or withdrawal of fluid is done slowly, a greatly dilated ventricular system can be emptied practically completely without any sensation on the part of the patient at the time of the evacuation of the fluid. Not rarely, however, the patient may have a severe headache a few hours later.

Furthermore, if one makes gentle but gradually increasing pressure in the suboccipital region of a patient on whom a suboccipital craniotomy has previously been performed, one can often bring on a frontal headache which may last for one or several hours.

It seems fair to conclude, from all of these facts, that sudden alterations of intraventricular pressure can produce a typical headache. It is of interest, in this connection, that I have never observed headache after lumbar puncture if there was a ventricular or arachnoid block in any location caudad to the third ventricle. Not a single patient with a complete spinal subarachnoid block from a spinal cord tumor ever had headache after the lumbar puncture. In 14 patients

with obstruction of the pathways for the cerebrospinal fluid caudad to the third ventricle in whom, for one reason or another—often through a lack of recognition of the true state of affairs—fluid was removed by lumbar puncture, no puncture headache occurred.

Recent experiences in three patients have led me to wonder whether sudden changes in pressure conditions within the third ventricle and in the optic thalami that form its lateral walls may be a factor in some varieties of headache. In two patients with brain tumor, there was a distension of one anterior horn as the result of a tumor which occluded the homolateral foramen of Monro and the body of the corresponding lateral ventricle. In both of these patients the rapid removal of fluid from the dilated and isolated anterior horn did not cause headache, but during the removal of fluid from the other lateral ventricle, severe headache was complained of.

The third patient had a tumor which compressed and obstructed both foramina of Monro and caused a dilatation of both lateral ventricles. The removal of fluid from both lateral ventricles and the injection of phenolphthalein and of air caused no headache, but the removal of fluid by lumbar puncture caused a severe puncture headache. In this patient, the pathways from the third ventricle to the lumbar subarachnoid space were patent, so that after the removal of fluid by lumbar puncture a change in pressure conditions within the third ventricle could occur.

Whatever may be the real significance of the facts I have described, they do seem to indicate that distension and stretching of the dura has probably little, if anything, to do with headache, but that sudden changes in intraventricular and perhaps intracranial pressure may have an important bearing upon the etiology of at least some varieties of headache.

CHAPTER II

PHYSIOLOGICAL MECHANISM FOR THE MAINTENANCE OF INTRACRANIAL PRESSURE

SECRETION AND ABSORPTION OF THE CEREBROSPINAL FLUID; THE RELATION OF VARIATIONS IN THE CIRCULATION¹

HUBERT S. HOWE, M.D.

AFTER more than a century of speculation, the ingenious experiments of Dandy in 1919 demonstrated without question that the main source of the cerebrospinal fluid is the choroid plexus. He was able to occlude both foramina of Monro in a dog and remove the choroid plexus from one lateral ventricle without disturbing the other. A few weeks later the animal was sacrificed and its brain examined. The ventricle with the intact choroid plexus was distended with fluid while the other was collapsed containing only a small amount of liquid similar in character to the blood plasma.

Cushing had previously observed the choroid plexus through a porencephalic communication with the lateral ventricle and had seen small drops of fluid appearing on its surface.

I have seen this "sweating" of the choroid by direct examination with a stereoscopic microscope in experimental animals. Undoubtedly, certain elements are added to the fluid after it leaves the ventricles either from the perivascular channels, which are in direct communication with the subarachnoid space, or by transudation through the walls of the capillaries on the surface of the brain. There is reason to believe that the contents of the perivascular spaces may be discharged into the subarachnoid cavity. In one instance of experimental encephalitis, I obtained a microscopic section showing a perivascular space longitudinally divided, and terminating at the surface. It was packed with cells but these were less crowded as the surface was approached and they were evidently being discharged into the subarachnoid cavity.

¹ From the Laboratory of Experimental Neurology, College of Physicians and Surgeons, Columbia University, New York.

If the perivascular spaces contribute to the cerebrospinal fluid, then their anatomical relations are important. These relations are by no means as clear as many writers have supposed. They are usually described as a simple invagination of the pia mater of the surface of the brain carried in around the blood vessels. Were this the case, the vessels on the surface of the brain would have no such sheath. This, however, is not the case, with the arterioles at least, for I have frequently been able to demonstrate a perivascular space in studying the cortex with a microscope. These spaces can be made to appear by decreasing the osmotic pressure of the blood, as a result of bleeding the experimental animal and infusing normal salt solution, or more simply by an infusion of distilled water.

The perivascular spaces are easily visible in experimentally produced encephalitis as I have frequently observed in rabbits. In some instances, simply stroking the vessels with a cotton swab will cause them to become visible. Possibly the simplest method of demonstration is to stimulate an arteriole with the faradic current. If this is done a sharp contraction is produced at the point of stimulation and for a short distance to either side. The perivascular space remains unaltered and outlines the former boundaries of the vessel. This contraction of the arterioles takes place without any distortion of the brain substance which would not occur were the vessels directly connected through their walls with the glial framework.

There has been much discussion as to the direction of flow of the fluid in the perivascular spaces. Is it from the interior of the brain to the surface as suggested by Weed, or in the reverse direction as believed by Mott? It is quite conceivable that under different conditions this flow, at most extremely small in amount, might occur in either direction. Thus the consensus of opinion apparently holds: that the cerebrospinal fluid is secreted by the choroid plexus, and that it receives certain accessions from the perivascular spaces.

ABSORPTION OF THE CEREBROSPINAL FLUID

More obscure even than the source of the cerebrospinal fluid, has been its destination.

It has been shown by Leonard Hill that the major part of the cerebrospinal fluid undoubtedly passes into the blood. He injected methylene blue in normal saline into the subarachnoid space and recovered some of it in the stomach, and in the urine within ten to

twenty minutes, while it did not appear in the lymphatics before an hour or more.

It is generally conceded that cerebrospinal fluid is being constantly formed, and various methods for determining the normal secretory rate have been undertaken. It is well known that large amounts of fluid may drain away within twenty-four hours in instances where there is direct connection from the subarachnoid space to the exterior. Many observers have injected water or saline into the subarachnoid space in the belief that in this way they could obtain an index of the normal absorption. Duret was able to inject 583 cc. of water into the cranio-vertebral cavity in two hours.

Falkenheim and Naunyn infused normal saline through a catheter into the conus at varied pressures. At a pressure of 15 mm. Hg there was some absorption, but it was slight. One cubic centimeter a minute was absorbed at a pressure of 59 mm. Hg.

Dandy found that 35 to 50 per cent of a dye injected into the ventricles was excreted through the urine in two hours. From this he concluded that the cerebrospinal fluid was absorbed at a similar rate. It is impossible, I believe, to make this deduction from this observation as certain substances dialyze from the cerebrospinal fluid into the blood with great rapidity while others pass but slowly, if at all. The conditions of all these experiments are so abnormal that it is doubtful if any reliable conclusion can be drawn from them as to the rate of secretion or absorption of the cerebrospinal fluid.

There is much to support the view that under normal conditions the exchange of cerebrospinal fluid is very slow. The difference in the contents of the fluid when obtained simultaneously from different loci would evidence a very sluggish circulation which would not be the case were the fluid undergoing rapid secretion and absorption. The slow diffusion and unequal distribution of foreign particles such as India ink when injected into the subarachnoid spaces point to the same conclusion. It is difficult to see how a rapid exchange of this fluid could serve any useful purpose, and as its main function seems to be a mechanical one, stability, with but very slow circulation or exchange, would seem more advantageous physiologically.

There are two main views regarding the pathways by which the cerebrospinal fluid reenters the circulation. The first hypothesis, and the one usually accepted at present, is that it is effected by passage through villus-like projections of arachnoid into the venous sinuses.

This conception is supported by the excellent work of Weed. The second view is that there is a direct passage of the cerebrospinal fluid into the blood by diffusion, according to the principles of osmosis. This latter supposition has been held by Mott, Dandy, Blackfan and others. While it is possible that both of these pathways are utilized, I believe that the main method of exit is directly through the vessel walls.

By the injection of colored gelatine into the subarachnoid space Key and Retzius demonstrated accurately the histological relationships of the arachnoid villi and Pacchionian bodies. They were shown to be bladder or cauliflower-like excrescences of the arachnoid, which occur mainly along the course of the dural venous sinuses, and frequently encroach upon the lumen of the main blood channel, or in lateral diverticulae. The arachnoid surface of the villi never lies free within the sinuses, and is not in direct relation with the blood.

The individual villi are sac-like herniations of the arachnoid which are traversed by a network of trabeculae. Over the summit of this elevation is a fine membranous covering derived from the dura. Between the arachnoid membrane and the dural sheath is an interval which is continuous with, and part of, the subdural space.

As demonstrating the possible means by which the cerebrospinal fluid reenters the blood important work has also been done by Weed. He injected potassium ferrocyanide and iron-ammonium citrate into the subarachnoid space. The brain was hardened in situ with a fluid containing 1 per cent hydrochloric acid. In this way Prussian blue granules were precipitated in the minute ramifications of the subarachnoid space. By this method he was able to study the anatomical relationships and structure of the arachnoid villi.

Those who hold that the cerebrospinal fluid escapes from the subarachnoid space into the blood by way of the arachnoid villi, believe that the passage is effected by seepage or filtration. It seems to me that this theory leaves much to be explained. In the first place the fluid in escaping from the surface of the villus would enter the subdural space and would subsequently have to pass through the dural membrane, which must offer some resistance even though it is attenuated in this locality.

Secondly, it is difficult to predicate how this seepage or filtration would be regulated or controlled. If one were to hazard an opinion as to the function of the arachnoid villi from their histological struc-

ture and relationship, it would seem more possible that they were concerned with the entrance and exit of the subdural fluid, than with the direct passage of the cerebrospinal fluid from the subarachnoid space into the blood.

In my work with hypertonic solutions in which I employed such solutions to determine their influence on intracranial pressure, I was amazed by the rapidity of the absorption of the cerebrospinal fluid under these conditions. Within three minutes after the injection of a concentrated solution the pressure would commence to fall and possibly within twenty to thirty minutes enough cerebrospinal fluid would have been absorbed to reduce the pressure to zero. It seemed unlikely that the blood had enough contact with the cerebrospinal fluid through the arachnoid villi to effect such a rapid absorption as this. It appeared much more probable that there was a direct passage of the cerebrospinal fluid into the cortical cerebral vessels where there is a large surface of contact. Weed had previously advanced this opinion as a result of his experiments. In order to determine the possibility of this direct passage, I made the following experiment.

A trephine opening about 2 cm. in diameter was made over the cerebral cortex in a cat under ether anesthesia. The dura was opened and reflected back to the margin of the bony aperture. The arachnoid was pressed against the cortex under the margin of the bone by the insertion of bone wax. With care and the use of a microscope, it is possible to do this without, at the same time, shutting off the circulation in the cortical vessels. In this way, the portion of cerebrospinal fluid covering the cortex in the exposed area, was cut off from communication with that in the remainder of the subarachnoid space. At this time the arachnoid bulged slightly and presented a smooth tense surface. Twenty cubic centimeters of a 1 per cent dextrose solution was then injected into the femoral vein. Within thirty minutes the arachnoid was no longer tense and even, but relaxed and irregular, draping over, and outlining the cortical vessels, thus demonstrating direct absorption of the cerebrospinal fluid into the blood. I have repeated this experiment many times, with similar results. It eliminated the participation of arachnoid villi as there were none in this locality.

The determination of the exact osmotic pressure of the blood and cerebrospinal fluid and their variations is beset with difficulties; and

but little work has been done in this field. While osmotic pressure has been considered to depend upon the number of molecules, ions, or other particles present, this has been shown by G. M. Lewis and others not to be entirely valid, especially in concentrated solutions. It, however, affords a working basis for judging the osmotic relations of the blood and cerebrospinal fluid. The quantities of the osmotically active substances in the blood and cerebrospinal fluid are given in table I. The figures are taken from Hamilton and from unpublished work of Atchley of the Presbyterian Hospital, New York.

It will be seen from these figures that the total electrolytes in the blood serum are somewhat greater than those in the cerebrospinal fluid.

In order to obtain further evidence of the osmotic relationship of these two fluids, I have made many direct determinations of osmotic

TABLE I
RELATIONSHIP BETWEEN ELECTROLYTES IN BLOOD SERUM AND CEREBROSPINAL FLUID*

TOTAL BASE		TOTAL ACID		PROTEIN		DEXTROSE		TOTAL ELECTROLYTES	
Blood Serum	Spinal Fluid	Blood Serum	Spinal Fluid	Blood Serum	Spinal Fluid	Blood Serum	Spinal Fluid	Blood Serum	Spinal Fluid
164.6	156.3	137.2	145.6	15	0.006	5.5	3.3	322.3	305.2

* Values in millimols per 1,000 grams of water. The figures are taken from Hamilton and the unpublished work of Atchley.

balance of the blood and spinal fluid of patients under normal conditions. For this purpose, the blood and cerebrospinal fluid were obtained simultaneously, and always after a fast of twelve hours. The osmotic pressure of the blood is undoubtedly at its lowest point at this time, it being subject to moderate variations due to the ingestion of sodium chloride, glucose, etc. The specimens of blood were agitated for ten minutes to prevent clotting.

Small osmometers were devised for this purpose and made as follows: A glass tube about 15 cm. in length and with a bore of 3 mm. was introduced through a rubber stopper into a test tube of 12 mm. diameter. The end of the small glass tube which was to be placed in the test tube was inserted into a specially prepared celloidin sac. The rubber cork was notched in order that the atmospheric pressure would be the

same in both tubes when the work was in position in the test tube. There is no artificial membrane which has the exact permeability of normal capillaries and different membranes have been used but celloidin membranes designated four B and six C after the formula of Krogh have been the ones mainly employed. The specimen of blood is placed in the small glass tube and celloidin sac, while the cerebrospinal fluid is placed in the test tube surrounding the dialyzing membrane. In this way I have produced an experimental capillary filled with human blood and entirely surrounded by human cerebrospinal fluid.

With these membranes separating the blood and cerebrospinal fluid for several days, there is an increase in the blood volume, at the expense of the volume of cerebrospinal fluid thus demonstrating a higher osmotic pressure in the blood. The passage of cerebrospinal fluid into the blood causes an elevation of the upper limit of the blood column which measures from 2 to 10 mm. or more during the first twenty-four hours. I have made in all twenty-one of these determinations, and while the amount of cerebrospinal fluid which has entered the blood has varied considerably in different instances, there has been no instance in which some of the fluid has failed to enter the blood.

If it is true that the osmotic pressure of the blood is greater than that of the cerebrospinal fluid, the cerebrospinal fluid must be constantly absorbed through the capillary walls with which it comes in contact unless the capillary membranes in this location are of different permeability than those of other portions of the body. There is no evidence of any such selective permeability under normal conditions, and so far as is known, absorption through the cerebral capillaries is subject to the same mechanism as it is elsewhere.

It may be argued that in case part of the subarachnoid space were completely walled off, the contained cerebrospinal fluid would be absorbed into the blood. This undoubtedly would take place if the walls of the dural cavity could collapse, but as this cannot occur, the fluid cannot be completely absorbed without something taking its place. Under these conditions, there gradually occurs an increasing concentration in the confined cerebrospinal fluid of substances which are normally present in the blood, until the character of the fluid becomes very similar to that of the plasma. How this is affected is not clear. In meningitis, there is an alteration of the capillary cells which normally act as a barrier between the blood and the cerebro-

spinal fluid, and this results in a passage of protein and other plasma constituents into the cerebrospinal fluid. This would, however, not explain the changes which take place in the fluid which is loculated by a tumor, and where there is no evident disease of the vascular endothelium.

It therefore seems probable that the cerebrospinal fluid is constantly diffusing through the thin walls of the capillaries and veins on the surface of the brain. The rate of diffusion is dependent upon the variations in the osmotic pressure of the blood. When the concentration of the blood is diminished or some of the constituents are decreased the rate of diffusion will be much less. Should the osmotic pressure of the blood fall below that of the cerebrospinal fluid, as it probably does in some instances in the early stages of pneumonia, where the chlorides are much reduced in the blood, diffusion will occur from the blood into the cerebrospinal fluid and the so called meningism will result.

The protein content of the blood is probably mainly responsible for its higher osmotic pressure as compared with the cerebrospinal fluid. Increase in the protein content in the cerebrospinal fluid will lessen this differential and reduce the rate of passage into the blood. For example in tuberculous meningitis, the cerebrospinal fluid contains a large amount of protein, and as a result of the decreased absorption into the blood, there is a great increase in the amount of fluid in the subarachnoid space and in the intracranial pressure.

A similar condition occurs if the osmotic pressure of the cerebrospinal fluid is raised by a hemorrhage in the subarachnoid space, or when an injection of the serum is made into the cerebrospinal fluid.

INTRACRANIAL PRESSURE

According to my observations and experiments, intracranial tension is a composite pressure dependent upon five major factors:

1. Volume of blood in brain and cord and coverings.
2. Volume of cerebrospinal fluid.
3. Volume of the cerebral axis.
4. Tension of vertebral dura.
5. Tension of skull.

Of these factors two are constant under normal conditions while the remainder are variable. The tension of the cranial dura is invariable on account of its relation to the unyielding walls of the skull.

The cerebrospinal axis may be distorted or displaced but is incompressible in the sense that it is not condensible.

In 1783 Monro advanced the view that the quantity of blood within the cranium is almost invariable. If this were true, the amount of blood entering through the arteries with each systole of the heart is exactly equalled by the amount returned through the veins. This gave rise to the question, "Was the circulation through the brain a constant, even flow or was it pulsatory?" The early physiologists who drew their conclusions from the observations of the fontanels in infants, adults with cranial defects, or animals with trephine openings in the skull, believed that the brain was subject to large expansile excursions with each heart beat. They all failed to appreciate that under these conditions (that is, fontanelle) there was only an elastic membrane instead of a complete, unyielding bony wall, and that variations in pressure against the skull could never produce movement or expansion. In the case, however, of intermittent pressure acting upon the dura unsupported by bone, pulsation would occur. Even Leonard Hill in his famous "window" experiment failed properly to evaluate the consequence of this modification. He placed a carefully sealed rubber tambour against the brain through an opening in the skull, and connected this tambour with a manometer in which the pressure was equal to the intracranial tension, but wholly overlooked the fact that in introducing an area which would respond to variations in pressure he had nullified the value of the experiment.

It seems clear that if any expansion of the dura were to occur, it would be confined to its spinal portion.

Duret was the first to demonstrate pulsation without altering the normal conditions through the introduction of an area of diminished resistance either by removing the bony support of the cerebral dura, or by making any communication with the cerebrospinal fluid through spinal or ventricular puncture. In Duret's experiment, a tambour was placed against the occipito-atlantal ligament, and pulsation, although very slight, was at one time evident. That this pulsation is slight may be judged from the fact that even when there is direct communication with the cerebrospinal fluid as in spinal puncture, the pulsatory movement of the fluid as observed in a manometer amounts to an oscillation of but 2 to 3 mm.

Cerebral pulsation has been supposed to favor the circulation of cerebrospinal fluid. Should this pulsation occur, it is difficult to see

how it would do more than produce a slight oscillatory movement of the fluid. With each expansion of the cerebrum a small amount of fluid would be expelled from the rigid cerebral cavity into the spinal canal. The expelled fluid would be accommodated by a distension of the spinal dura, but with cerebral relaxation it would be returned to the cerebral cavity. Foreign particles in the subarachnoid space, such as red blood cells or particles of carbon when observed with the microscope show no oscillatory or other movement. It is therefore my belief that the pulsatory movement of the cerebrospinal axis under normal conditions is extremely slight and of little physiological importance in effecting the circulation of the cerebrospinal fluid.

In order to understand the dynamics of intracranial pressure, one should first visualize the intradural cavity without the brain or spinal cord in situ. This cavity is composed of two parts, the cerebral portion, a large but unyielding space connected with a spinal arm which is partially elastic and allows of some distension. If such a simple chamber were filled with fluid until the distensible portion were moderately stretched, a pressure equal to that applied to the fluid by the elastic membrane would be transmitted equally to every point of the chamber. The pressure at any given point would be the thrust of the stretched membrane plus the pressure of the head of fluid above it. This explains the difference in intracranial pressure recorded in the upright and prone positions and also the variations produced by stretching or relaxing the spinal dura effected respectively by flexion or extension of the spine.

According to my measurements, the patient in the lateral, recumbent position shows a manometric elevation of cerebrospinal fluid averaging 150 mm. In the sitting position this elevation is increased to 450 mm., the difference between the two being 300 mm. This corresponds to the actual height of the column of fluid from the cisterna magna to the point of lumbar puncture, namely 30 cm. (This is, of course, a vertical measurement, and not the length of the spine.)

This analogy, however, cannot be carried far as the conditions in the cranio-vertebral cavity are by no means as simple as this, for here we have in the center of the cranial cavity an incompressible mass, through which the blood is circulating constantly, as well as a series of compartments which are more or less separated from each other.

The blood enters the brain through the large arteries at a constant pressure of about 900 mm. of water. This rises to a pressure of 1500 mm. with each systolic contraction of the heart. As the arterioles

decrease in size and increase in number, the pressure gradually falls on account of the increased friction to which the circulating fluid is subjected. The pressure in the veins averages about 150 mm. of water, while the capillary pressure is 10 to 20 mm. higher. The capillary pressure is thus in closer relation to the venous, than to the arterial pressure.

In order to study the pressure in the vessels, I have drawn out glass tubing of an original diameter of 2 mm. into small capillary points. With the aid of a microscope they can be inserted into some of the smaller arterioles and venules of the brain and the pressure measured by the method employed by Krogh. Under the conditions of this experiment, the lack of support naturally afforded the vessels on the surface of the brain and the rapid clotting of the blood, makes this procedure unsuitable for observations of more than a few minutes duration. I have been able, by this method and others, to demonstrate the following facts:

1. Under normal conditions the pressure of the blood in the cerebral venous sinuses is practically the same as the cerebrospinal fluid pressure. In the human subject the cerebrospinal fluid pressure recorded through spinal puncture in the lumbar region, with the patient in the lateral position, is practically the same as the venous pressure at the elbow.

2. Increase in the arterial pressure, as produced by clamping the abdominal aorta produces a slight temporary rise in intracranial pressure and in the cerebral venous pressure, but its main effect is to increase the rate of blood flow.

3. A much greater rise in intracranial pressure is afforded by compression of the veins or by producing any impediment to the venous outflow. While increasing the arterial pressure may momentarily and slightly increase the amount of blood in the cerebral circulation, it cannot possibly do so to the extent that obstruction to the outflow will.

Compression of the jugulars inhibits the escape of blood from the skull, and the increased volume of blood in the dural cavity resulting from this procedure causes a rise in the intracranial pressure.

Obstruction to the general venous outflow is produced mainly in three ways:

1. Experimental compression of the jugulars.
2. Compression of the right auricle, by coughing, straining or any act producing a rise in the intrathoracic pressure.

3. A generalized rise in intracranial pressure whether through increase in the amount of fluid in the subarachnoid space, or the ventricles; enlargement of the cerebrospinal axis, or decrease in the volume of the dural cavity.

If the escape of blood from the cranial cavity is impeded through moderate compression of the cerebral venules, the events produced by this obstruction are as follows:

1. Compression of the veins, resulting in a slowing of the velocity of circulation, and a decrease in the volume of output.

2. This stasis in the veins produces a rise in the pressure in the capillaries sufficient to overcome this obstruction and a resumption of the circulation. As the constant arterial pressure is about six times the venous pressure, it is evident that the venous and capillary pressure can rise greatly without approaching that of the larger arteries. Should the compressing force, however, rise high enough to approach the level of the arterial pressure, there is a rise in the general arterial tension.

It may be seen therefore that a moderate increase in the subarachnoid pressure is quickly balanced by a similar augmentation of venous and capillary pressures. As a result of this rise in pressure, there is not alone a continuance of the normal circulation but also there is no distortion of the surrounding nerve tissue, which would be the case were the blood in the vessels expressed from their normal spaces. This mechanism is therefore of utmost importance in the maintainance of the normal physiological functions. As this is the case, moderate variations in subarachnoid pressure are unimportant, and there is no sharply defined normal level in the sense that any exact and unvarying pressure must be maintained for the continuance of the normal physiological processes. This compensating mechanism, which insures an adequate circulation despite an increase in intracranial tension, explains the possibility of the normal functional operation of the central nervous system for continuous periods, in the presence of considerable increase in intracranial pressure. It must be understood, however, that this mechanism is exercised only when the compressing force is applied in such a way as to cause an obstruction to the general intracranial circulation.

4. Artificial lowering of the intracranial pressure by the removal of cerebrospinal fluid through subarachnoid puncture, or by the intravenous injection of hypertonic solutions into the blood stream produces within certain limits a corresponding decrease in the venous pressure.

Theoretically, there might be a reciprocal variation in the volumes of blood and cerebrospinal fluid within the dural cavity. Increase in the amount of cerebrospinal fluid might be compensated for by an equal diminution in the blood in the cerebral circulation. It has been shown, however, in the preceding discussion that this is not the case, at any rate when the volume of increment of cerebrospinal fluid is not large. Were there a decrease in blood volume equal to the accession of cerebrospinal fluid, there would be obviously no increase in intracranial tension, and a distortion of the nerve tissue due to the alterations in special relationship would result.

Up to this time we have been considering the relationships of generalized increased intracranial tension. A local compressing force may have from the first two consequences. First, from the addition to the volume of matter within a closed space, it may cause a generalized increase in pressure with its eventualities. Second, through local compression it may obliterate, or impede the circulation in the veins and capillaries within its immediate vicinity. This stasis will not of itself cause the increase in back pressure noted in a generalized increase in intracranial tension, as there is little or no obstruction to the general venous outflow.

If the mass of the compressing element is large enough to cause an increase in intracranial tension, with a rise in pressure in the head waters of the circulation, it may be of local advantage, as this increased vis a tergo may aid in the reestablishment of the circulation in the locally compressed vessels.

As long as the brain is surrounded by a continuous mantle of fluid, the pressure relationships of a hydraulic chamber continue, and the brunt of the local pressure effects may be somewhat modified by the general increase in intracranial tension. This is one of the reasons why the general symptoms of intracranial pressure so frequently antedate the focal manifestations in instances of tumor.

When, however, in the case of neoplasm, the local enlargement of the brain becomes sufficient to fill its dural chamber and express the fluid from its position over the cortex, the hydraulic principle fails, and the pressure in this chamber can no longer be measured by the pressure of the cerebrospinal fluid obtained through spinal or cisternal puncture. At this period the local circulation may be seriously impaired and focal symptoms rapidly develop.

We have so long considered the serious effects of cerebral compres-

sion that we may lose sight of the fact that normal function may continue for long periods with considerable elevation of intracranial pressure. This is the case when the pressure is equally applied and the free circulation of the cerebrospinal fluid is unimpaired, as may occur in serous meningitis. It is the uneven application of pressure which gives rise to distortion with the local circulation, rather than actual increase in tension which is mainly responsible for pathological changes. The one locality where distortion and compression may occur with increased intracranial pressure even though the pressure is evenly applied within the skull is, of course, the optic nerve. Here the anatomical relationships are such that it is impossible to balance the increase in pressure within the cranium by a similar force over the nerve head.

In this connection it may be noted that the diagnostic localization of tumors will continue to be imperfect until we more fully realize that in many portions of the brain the infiltrating neoplastic cells produce little or no local destruction of the nerve elements. The actual physiological disturbance being due to distortion and alterations of the circulation. It is these remote distortion effects which account for the extensive physiological disorganizations so frequently seen in the late stages of brain tumor. More study must be given to the arrangement of the vascular structures of the central nervous system and to the distant deformities resulting from the neoplastic enlargement of individual portions of the brain.

SUMMARY AND CONCLUSIONS

1. The cerebrospinal fluid is secreted mainly by the choroid plexus, but also receives some additions from the perivascular channels communicating with the subarachnoid space on the surface of the brain.
2. The cerebrospinal fluid is re-absorbed into the blood by diffusion through the vessel walls. This is effected by the difference in the osmotic pressure of the two fluids.
3. In inflammation of the meninges there is a disorganization of the capillary cells which are ordinarily impermeable to certain substances in the blood with the result that they pass into the cerebrospinal fluid.
4. The normal pressure is maintained by the secretion of sufficient cerebrospinal fluid to moderately distend the spinal dura.
5. The intracranial pressure is roughly equal to the venous pressure

and within limits variation in the pressure in either the cerebrospinal fluid or the venous blood is accompanied by similar directional pressure changes in the other fluid.

6. The normal cerebral arterial pressure is about six times the venous pressure. Increasing the intracranial pressure by augmenting the amount of fluid in the subarachnoid space, causes a compensating rise in the venous pressure. This in turn causes a rise in the capillaries and arterioles, and eventually in the general arterial pressure.

7. As a result of this compensatory mechanism, the cerebral circulation can be maintained when the intracranial pressure is increased.

DISCUSSION

The following questions submitted to Dr. Howe before the Commission, together with the answers to them, are here reported verbatim.

DR. FREDERICK TILNEY: I should like to ask Dr. Howe several questions covering this work. First, I should like to know whether he has any direct observation from his own experience to show that the perivascular spaces contribute to the cerebrospinal fluid. I think this is a very important point. Heretofore we have attributed the source of the fluid almost exclusively to the chorioid glands and he states that he believes the perivascular spaces contribute to the fluid. I would like to know if he has any direct observations covering this point.

DR. HOWE: In one instance, Dr. Tilney, I obtained a section of the cortex in the case of experimental encephalitis presenting a vein which was cut longitudinally passing from the interior to the surface. The perivascular space was packed with cells. These were very densely packed deep in the cortex but, as it approached the surface, they became less dense and were apparently being discharged into the subarachnoid space.

DR. TILNEY: Have any of your experiments given you a conception of the rate of secretion and absorption of the fluid?

DR. HOWE: None of my experiments, Dr. Tilney, have given me any definite idea as to this, but the consensus seems to be, that the secretion is rather rapid. I think there is much to support the view that under normal conditions it is slow. In the first place, the difference in composition of the fluid obtained simultaneously from different loci would evidence a slow circulation, and secondly, if one injects foreign particles under the subarachnoid and watches them with the microscope, there is very little movement, showing a very inactive circulation, and also it is difficult to see how a rapid change in a fluid whose main function appears to be a mechanical one would be physiologically advantageous, so I think the exchange is probably quite slow.

DR. TILNEY: Do you think there is any valid evidence that the arachnoidal villi will participate in the passage of the fluid into the blood stream?

DR. HOWE: I have never seen any evidence of it.

DR. TILNEY: That is a very important point.

DR. HOWE: I have never seen any evidence that it passes through the arachnoidal villi. I think it passes directly through the walls of the veins into the circulation.

DR. TILNEY: Have you experimental evidence to substantiate that view?

DR. HOWE: I have, that it passes directly through the walls of the capillaries, but none that it passes through the arachnoid villi.

DR. TILNEY: In this artificial capillary of yours that you constructed, is there anything to show that the vessel approximates the normal conditions of the capillary bed in the brain or elsewhere in the body?

DR. HOWE: Of course the permeability of the capillaries does vary under different conditions, everyone is familiar with the edema that may develop in the skin, after exposure to heat or cold, or in intoxications with alcohol and protein poisons, there is unquestionably a variation in the permeability of the capillaries.

These membranes were prepared after the work of Krogh, who demonstrated that the membrane as I prepared it here, very nearly approached the permeability of human capillaries.

DR. GEORGE B. HASSIN: In a brain with extensive hydrocephalus and an atrophied choroid plexus, how could the spinal fluid form?

DR. HOWE: Probably in the same way that an atrophic kidney secretes urine.

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CHAPTER III

EXPERIMENTAL STUDIES OF INTRACRANIAL PRESSURE¹

LEWIS H. WEED, M.D.

THE problems centering about the pressure of the cerebrospinal fluid seem in the main to be relatively simple if one consider only the normal level of this pressure. But, when one takes into account the various factors concerned with the maintenance of this pressure, the problems become far more complicated; and while recently much progress has been achieved, there still remain a multitude of unanswered questions to which the investigator must turn his energies. The situation in regard to the pressure of this fluid is therefore quite similar to that existing in many other problems of anatomical physiology: the problem here is not solely one of function, but also is one of morphology. It is intimately concerned with the anatomy of the membranous and bony coverings of the central nervous system.

ANATOMY OF THE MENINGES

It may profit to review briefly present-day knowledge of the coverings of the central nervous system, particularly in their relation to the fluid-channels. Closely adhering to the brain is the pia mater, a delicate membrane enveloping an elaborate and dense network of arteries and veins. Extending outward from the pia mater are the arachnoid trabeculae—delicate, cellular structures occasionally having a fibrous or vascular core. These trabeculae spread out upon the second of the coverings of the nervous system—the arachnoid membrane—to which they are usually assigned. Like the pia, the arachnoid is delicate, but instead of extending into all of the sulci of the central nervous system, this membrane bridges these furrows and constitutes everywhere an intact cellular structure over the whole central nervous system. The outer surface of the pia mater, the arachnoid trabeculae, and both surfaces of the arachnoid are covered by a continuous cell-layer of a flat, polygonal mesothelium. The

¹ From the Department of Anatomy, Johns Hopkins University.

third of the membranes of the central nervous system is the dura mater. This membrane is tough and fibrous; it is inelastic in character and is covered only on its inner surface by the mesothelial cells.

Between the arachnoid and the pia, in the subarachnoid space, circulates the cerebrospinal fluid, after this characteristic body-liquid has taken origin from intraventricular structures. As a factor in the maintenance of the cerebrospinal fluid pressure, the dura mater assumes first importance because of its inelastic character, but this membrane has almost no relation to the normal circulation of the fluid. This is due to the fact that the subdural space under normal conditions is merely a potential cavity, the inner surface of the dura being separated from the outer surface of the arachnoid membrane by a capillary layer of fluid. Functionally therefore, the subarachnoid space is the one concerned in the particular problem of the cerebrospinal fluid.

NORMAL PRESSURE OF THE CEREBROSPINAL FLUID

It has been known for many years that the cerebrospinal fluid is under positive pressure—an observation dating back to the epoch-making studies of Magendie (25). For it was Magendie who first noticed that the occipitoatlantoid membrane pulsated when the fascial and muscular layers were removed. On incising the membrane, Magendie noticed the escape of clear watery fluid, which he termed "*le liquide céphalo-rachidien*." Following Magendie there passed a long period during which but few observations of importance were made upon cerebrospinal fluid; but with Key and Retzius' (21) publications in the 1870's, new knowledge began to be rapidly accumulated and in the past fifty years an enormous mass of reliable data has been presented by workers in many fields of related interests.

The initial observations of Key and Retzius indicated that, in dogs under ether, positive pressures of 162 to 216 mm. of water occurred in the cerebrospinal fluid during inspiration, while during expiration pressures of 216 to 270 mm. of water were recorded. Bergmann (3), in his first paper, announced that pressures of 80 mm. in narcotized dogs were apparently normal, but in a later publication (4) he gave the normal pressure in narcotized dogs as 120 to 160 mm. of salt solution. Falkenheim and Naunyn (13) stated 100 to 150 mm. of water to be the normal pressure in curarized dogs, while Leyden's (24) observations indicated that 80 to 150 mm. of water constituted the

normal level in unetherized dogs and 100 to 120 mm. of water in dogs under morphine. Leonard Hill (17) felt that the pressure of the cerebrospinal fluid was under most conditions at a constant level but, that with changes in posture, pressures from zero to 50 mm. of mercury would occur in human beings.

Almost all of these readings were made by direct manometric methods and the results, omitting Leonard Hill's assumptions for the moment, indicated that the normal pressure of the cerebrospinal fluid was in the neighborhood of 120 to 125 mm. of water, though individual variations from animal to animal occurred. Dixon and Halliburton (8) used a graphic method for recording the pressure, employing animals under morphine-urethane anesthesia. They gave a rough average of 40 to 70 mm. of salt solution as the normal pressure of this fluid in the dog, but they noted extreme variations of the normal pressure under their experimental conditions. The following values given by these investigators for five-minute intervals in one animal are quite typical of the variations under their experimental conditions: 95, 25, 30, 35, 55, 25, 80, 65, 65, 75, 70, 60, 55, 50, 80, 90 mm. of 10 per cent solution of sodium citrate.

Such extreme variations have not been noted by any of the American observers who in the past ten years have devoted themselves to study of this subject. With McKibben, the writer (40) obtained an average of 119 mm. of cerebrospinal fluid in etherized cats immediately after the connection of the manometer with a needle in the subarachnoid space. This pressure, if read somewhat later, was found to average 129 mm., the rise apparently being due to replacement of the cerebrospinal fluid displaced in the manometer. Becht (2) reported an average pressure of 112 mm. in animals under intratracheal ether, while Foley and Putnam (16) recorded an average of 127 mm. for the normal reading in animals under ether. Foley and Putnam's average value for initial readings on 100 cats under various anesthetics was 133 mm. of cerebrospinal fluid. In the second series of observations with Hughson, the writer (37) reported an initial average pressure of 119 mm. of cerebrospinal fluid obtained from 77 cats under ether administered by the Woulfe bottle, the maximum value being 159 mm. and the minimum 83 mm. of fluid. More recently, Howe (18) found an average pressure of 127 mm. in an experimental series of cats.

Assuming then that the average pressure of the cerebrospinal fluid

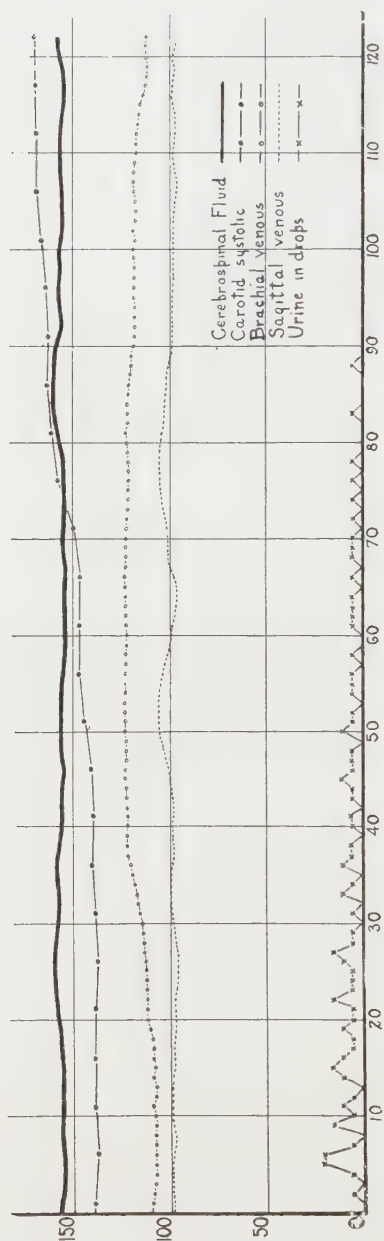


FIG. 1. Dog (experiment 113). Ordinates represent millimeters of Ringer's solution or mercury (carotid pressure); abscissae represent time in minutes. Control observation for experimental conditions under ether anesthesia to show range of pressure-variation. Cerebrospinal fluid pressure obtained from occipito-atlantoid manometer; animal in horizontal position.

in anesthetized laboratory mammals is approximately 125 mm. of fluid, it is interesting to note the type of pressure-fluctuations reported. Becht (2) is the only American observer to report fluctuations of marked extent in the normal pressure of the fluid. It has become quite obvious that these wide fluctuations in anesthetized animals, as first reported by Dixon and Halliburton, are the result of fluctuations in the experimental conditions, particularly of changes in the concentration of anesthesia. Under well controlled experimental conditions, as shown by the writer with McKibben and later with Hughson, the pressure of the cerebrospinal fluid does not vary more than 10 mm. in periods of one to four hours, the curve of readings being almost constant and showing but slight change in one or another direction around a mean characteristic of that animal (fig. 1). If, however, the anesthetic is markedly changed in concentration, wide fluctuations occur and the greatest diversity of experimental result may be obtained. It seems, therefore, that the normal pressure existing in well etherized animals and hence by inference in animals under quiet conditions of life is fairly constant, subject to but slight variation if the posture of the animal remains unchanged.

FACTORS CONCERNED IN THE MAINTENANCE OF CEREBROSPINAL FLUID PRESSURE

Realizing that the cerebrospinal fluid is a distinctive body-fluid, it becomes essential to inquire into the factors which contribute to the maintenance of the normal positive pressure of this fluid. It is almost universally granted by observers that the choroid plexuses in the cerebral ventricles produce by far the major portion of the fluid. It is not, however, within the scope of this paper to inquire into the processes by which these cells elaborate the fluid: whether the process is one of secretion, of selective filtration, or of ordinary filtration is quite beyond the point. It is, however, apparent that in some way a positive pressure is imparted to this fluid and one quickly assumes that such a positive pressure must be related to the balance between production and absorption of the fluid, to the elasticity of the dura mater, to hydrostatic pressures, or to the pressures within the cerebral arteries and veins. The many investigations on this subject have all led to the conclusion that the pressure of the fluid is dependent upon these factors to various degrees and in various combinations, but the exact significance of these relationships is not thoroughly understood.

Presentation of the experimental data will serve to establish certain conclusions in this regard and to point out the unsolved questions.

Balance between production and absorption of the fluid

It is obvious that the processes of production and absorption of the cerebrospinal fluid must be in quantitative balance in the normal state. But such a quantitative balance does not eliminate the possibility that the cells of the choroid plexuses maintain a "secretion-pressure" which is distributed by the cerebrospinal fluid throughout the meningeal spaces. Such a positive secretion-pressure might be thought necessary for the normal process of absorption of the fluid into the blood-stream. There is evidence of an experimental nature indicating that filtration plays an important rôle in the mechanism of drainage of the fluid into the venous system, though participation of the factors of osmosis and diffusion has not been excluded (Weed (34, 36)). The chief argument in favor of filtration playing an important part in the process of absorption is based upon the well-established fact that the higher the pressure of introduction the more fluid is absorbed from the subarachnoid space (Spina (30, 31, 32, 33), Falkenheim and Naunyn (13)). Hence it is wholly possible that the secretion-pressure of the cells of the choroid plexuses is essential for the absorption of the fluid, but whatever the theoretical attractiveness of this conception, it must be confessed that we have no reliable data in support. The question of secretion-pressure necessarily becomes involved with the problems of the vascular pressures.

Elasticity of the dura mater

In a discussion of the factors concerned in the maintenance of the normal pressure of the cerebrospinal fluid, Pfaundler (27) considered that the elasticity of the meninges contributed 8 per cent of the total. This factor however seems to be greatly over-emphasized in this estimate, particularly when viewed critically from the anatomical standpoint. The dura mater is a tough, almost inelastic membrane which in the cranial region is tightly adherent to the bones of the skull. It is almost impossible to stretch the dura to any extent, as it is made up almost entirely of white fibrous tissue. As the arachnoid is applied closely to the dura, being separated everywhere by a capillary layer of fluid, the elastic quality of this leptomeninx can hardly play any rôle in contributing to the elasticity of the meninges.

When one gives consideration to the low normal pressures existing in the subarachnoid space (100 to 150 mm. of normal salt solution), it seems somewhat absurd to think that the tough fibrous dura could be so stretched by the fluid under its low tension as to contribute an element of elasticity to the maintenance of pressure. It would seem wiser to revert to the "resiliency of the brain" under tension as first advanced by Burrows (5) in 1846.

Hydrostatic pressures

The importance of this factor is of course apparent in any determinations of cerebrospinal fluid pressure in positions other than the prone. In observations on four-footed laboratory mammals, this factor is of minimal significance as under standard experimental conditions the pressure-determinations are taken with the animals in the horizontal position. Even here, however, there is usually a small hydrostatic influence theoretically possible since one cerebral hemisphere lies above the puncture-needle if the animal be placed upon its side. But in clinical observations, due regard must be paid to this factor, as pressures of the cerebrospinal fluid obtained from patients lying prone or sitting upright show marked differences, the customary readings showing an increase of approximately 200 mm. of fluid in the erect posture over the prone (Barré and Schrapf (1), Zylberlast-Zand (43)). This phase of the problem will be discussed under the heading of the effect of posture upon the pressure of the cerebrospinal fluid.

Cerebral arterial pressure

Many physiological observations upon the pressure in the cerebral arteries have been made; the method, which is simplest and yields apparently excellent results, is the indirect procedure of taking the pressure of the common carotid artery just below the bifurcation and with the external carotid ligated. This method gives a reading of internal carotid pressure directly through the circle of Willis. Intracranial arterial pressure obtained in this way varies but little from that of the ordinary common carotid pressure. The variations are always in the same direction and are of slightly lesser extent. Such a method, however, gives merely the pressure of the largest arteries at the base of the brain and yields almost no information regarding pressures in the smaller arteries.

From findings based on such methods of determination it is fair to assume that the intracranial arterial pressure is approximately 100 to 120 mm. Hg., if the normal systemic pressure in the animal varies between 110 and 140 mm. Hg. This arterial pressure does not, however, give exact data regarding the pressure which is essential for our particular problem; that is, the pressure existing in the fairly wide capillaries of the choroid plexuses. On the basis of deductions, both direct and indirect, it may be assumed that the pressure in the capillaries of the choroid plexuses ranges from 30 to 60 mm. Hg.—a pressure far in excess of that of the cerebrospinal fluid. Thus, between the cerebral (choroidal) capillary and the cerebrospinal fluid, there is a drop of 30 mm. Hg. in pressure. It follows therefore that the pressure of the cerebrospinal fluid can bear only an indirect relationship to the pressure of the cerebral arteries.

But this pressure in the cerebral arteries has a very important, even though indirect, relationship to the pressure of the cerebrospinal fluid. In the course of many observations on combined cerebral arterial and cerebrospinal fluid pressures it has been noted that small variations of 10 to 20 mm. Hg. in the arterial pressure may occur slowly, without any change in the pressure of the cerebrospinal fluid. Wide variations in the carotid arterial pressure, however, affect markedly the pressure of the cerebrospinal fluid. A sudden and marked rise in the arterial pressure causes a sharp increase of corresponding degree in the pressure of the cerebrospinal fluid; conversely, a sharp fall in the arterial pressure causes a similarly sharp fall in the pressure of the cerebrospinal fluid.

It becomes of interest, therefore, to ascertain whether this fall or this rise in pressure of the cerebrospinal fluid, following such changes of the arterial pressure in the same direction, are related directly or indirectly. On this subject we have relatively little information, although a mass of data is available to show an indirect relationship. An increase in intracranial arterial pressure of 50 mm. Hg. causes an analogous increase in the cerebrospinal fluid pressure. The increase in the fluid pressure is, however, immediate and cannot be related to an increased elaboration of fluid, due to the heightened arterial pressure. But another factor comes into play in such increases in fluid-pressure—the factor of intracranial blood volume. Regarding this factor, there are practically no data available.

On the basis of the findings at hand, it seems fair to conclude that

the pressure of the cerebrospinal fluid is relatively independent of that of the cerebral arteries; this independence is however in no sense complete. With minor alterations in cerebral arterial pressure, slowly effected either experimentally or under normal physiological conditions, the pressure of the cerebrospinal fluid is maintained at its customary levels and is not altered. When however gross changes in cerebral arterial pressure occur rapidly, the pressure of the cerebrospinal fluid is changed, always in the same direction and usually in a proportionately lesser degree. It is also apparent that with advancing age, both in animals and man, with the concomitant increase in arterial tension, the pressure of the cerebrospinal fluid increases. But no demonstration that this pressure-increase in the fluid is due primarily to pressure-increase in the arteries has been made.

Intracranial venous pressure

Knowledge of the relationship of the cerebrospinal fluid pressure to intracranial venous pressure was first brought forward by the experiments of Leonard Hill (17), though some observations had been made previously. Hill devised a method for the simultaneous recording of the cerebrospinal fluid pressure and of the intracranial venous pressure in the torcular Herophili. The method of procedure for obtaining this venous pressure was quite simple, consisting in making a small trephine opening through the occipital bone into the torcular and connecting the torcular blood through an appropriate cannula to a recording mechanism. Using this technique, Leonard Hill found that under practically all conditions the pressure in the torcular and that of the cerebrospinal fluid were identical. Variations might occur in either of these pressures but similar variations of the same extent occurred simultaneously in the pressure of the other fluid.

These observations of Leonard Hill on the equivalence of the two pressures were accepted for approximately twenty years. This idea of equality of the pressures was abandoned only when Dixon and Halliburton (3), using an almost identical method of experimental procedure, found the two pressures to be dissimilar. Dixon and Halliburton ascertained that under some conditions the pressure of the cerebrospinal fluid exceeded that in the torcular; under other conditions the pressure in the torcular exceeded that of the cerebrospinal fluid. As a result of many observations, Dixon and Halliburton came to the conclusion that the pressure of the cerebrospinal fluid under most conditions was less than in the cerebral veins.

At about the same time, Wegefardth (42) reported experiments on a series of kittens, in which he established a free communication between the superior sagittal sinus and the subarachnoid space. In these animals, after a period of several days or several weeks, no apparent bleeding into the subarachnoid space occurred, and if the animal was killed by gas or ether this condition held universally. If, however, cerebrospinal fluid was removed by puncture shortly before killing the animal and the animal was then embalmed without opening the cranium, the subarachnoid space was found to be filled with blood. Such a finding as that reported by Wegefardth seemed to throw doubt on Dixon and Halliburton's general thesis that at most times the pressure of the cerebral venous system exceeded that of the cerebrospinal fluid. And there were other arguments also in favor of the idea that the cerebral venous pressure was at a lower level than that in the cerebrospinal fluid.

Becht's (2) experiments, published some years later, were in some respects at variance with those of Dixon and Halliburton, though they confirmed the general contention of inequality of cerebral venous pressure and cerebrospinal fluid pressure. Becht felt that the cerebrospinal fluid pressure was dependent upon both intracranial arterial and venous pressures, though it was not identical with either. His data indicated that the cerebral venous (torcular) or the cerebrospinal fluid pressure might be the higher but that usually the former exceeded the latter.

The observations of Dixon and Halliburton and of Becht were made under almost identical experimental procedures. These procedures involved slight modification of Leonard Hill's original method for the determination of the cerebral venous pressure in the torcular Herophili; they possessed, however, inherent difficulties for sound physiological observations. The very wide divergencies in the normal pressures reported by this method (13 to 601 mm. in one series) indicated that technically the method was subject to extreme limitations. With these difficulties in mind, Hughson and the writer (39) devised a new method for the recording of cerebral venous pressure in the superior sagittal sinus. Making a narrow gutter in the vault of the cranium in the mid-line, it was found possible to expose the external dural surface of the superior sagittal sinus without injury and to slip an appropriate needle into the sinus posteriorly, so that the end of the needle came closely into contact with the expansion

of the sinus in the torcular region. This needle was then connected with a manometer and direct readings of the pressure in the sinus were made. The procedure possessed one extreme advantage over previous methods in that the pressure of the cerebrospinal fluid could be taken during the introduction of the sinus-needle. In this way it was possible to observe directly any alteration in the pressure of the cerebrospinal fluid caused by the introduction of the sinus-needle. Under ordinary conditions of experimentation no change in the cerebrospinal fluid occurred on introduction of the sinus-needle, thus demonstrating that no venous back-flow had occurred and that the readings obtained were reliable indices of the actual pressures in the cerebral veins.

Using this method, Weed and Hughson (39) found that under almost all conditions the pressure of the cerebrospinal fluid exceeded that of the sagittal sinus, being customarily considerably above that of the veins (5 to 50 mm.). They presented data which indicated that alteration in the intracranial venous pressure effected alterations in the pressure of the cerebrospinal fluid in the same direction but of lesser magnitude. And conversely it was shown, in agreement with Dixon and Halliburton, that within the physiological limits tested alteration in the pressure of the cerebrospinal fluid caused variations in the pressure of the sagittal venous sinus of lesser extent but in the same direction.

The relationship then between intracranial venous pressure and that of the cerebrospinal fluid is close but it is fair to assume that under normal conditions the pressure of the cerebrospinal fluid exceeds that of the cerebral veins, though alterations in either of these pressures effect alterations of similar direction but of lesser extent in the other system. There is, under ordinary circumstances, no identity of these two pressures. The pressure of the cerebrospinal fluid may therefore be considered to be an independent pressure of a body-fluid, though affected by changes in the pressure of the cerebral arteries and of the cerebral veins.

EXPERIMENTAL MODIFICATION OF THE CEREBROSPINAL FLUID PRESSURE

Since Cappelletti's (6) discovery in 1900 that variations in ether concentration cause variations in the rate of expulsion of cerebrospinal fluid from a subarachnoid cannula, many observations on the effect of drugs on the rate of production of the cerebrospinal fluid have been

made. All of the earlier observations dealt with the rate of expulsion of fluid from an experimental cannula and until the introduction of more rigid methods of control, largely by Dixon and Halliburton (8), a simple increase in the rate of expulsion of the fluid was assumed to represent an increase in the rate of production. Dixon and Halliburton measured the pressure of the cerebrospinal fluid in relation to the pressure in the torcular Herophili and ascertained that certain extracts (particularly, of chorioid plexus and brain substance) increased the pressure of the cerebrospinal fluid without corresponding increase in the pressure of the cerebral veins. This was taken by them to demonstrate an increased production of fluid. As pointed out by the writer (35) some years ago, practically all of the observations made on this particular subject must be discarded because of the fact that all are based on the idea that the blood and the cerebrospinal fluid are the only two variable elements within the bony containers of the central nervous system. But, with the demonstration that the brain under definite experimental conditions can be altered in volume (Weed and McKibben (41)), this particular problem of the cerebrospinal fluid needs to be reviewed.

The experimental modification of the pressure of the cerebrospinal fluid by means of intravenous injection of solutions of various concentrations seems to offer opportunities for well-controlled experiments along this line. In 1919, working with McKibben, the writer (40) was able to show that the intravenous injection of a strongly hypertonic solution markedly lowered the pressure of the cerebrospinal fluid, frequently producing negative readings of as great extent as the positive values previously existing in the animal (fig. 2). The maximum effect of such intravenous injections was achieved in twenty-five to thirty-five minutes after the cessation of injection; the effect persisted for several hours with gradual recovery.

Conversely, if a hypotonic solution (distilled water) was injected intravenously in large amount, the pressure of the cerebrospinal fluid was found to increase sharply and to assume levels far in excess of the normal pressures (fig. 3). This effect, likewise, reached its maximum in twenty-five to thirty-five minutes after the end of the period of injection and it persisted for several hours, with gradual recession to normal levels. If, however, an equally large or even larger quantity of Ringer's solution, or of any isotonic solution, was injected, a temporary rise in the pressure of the cerebrospinal fluid of slight extent

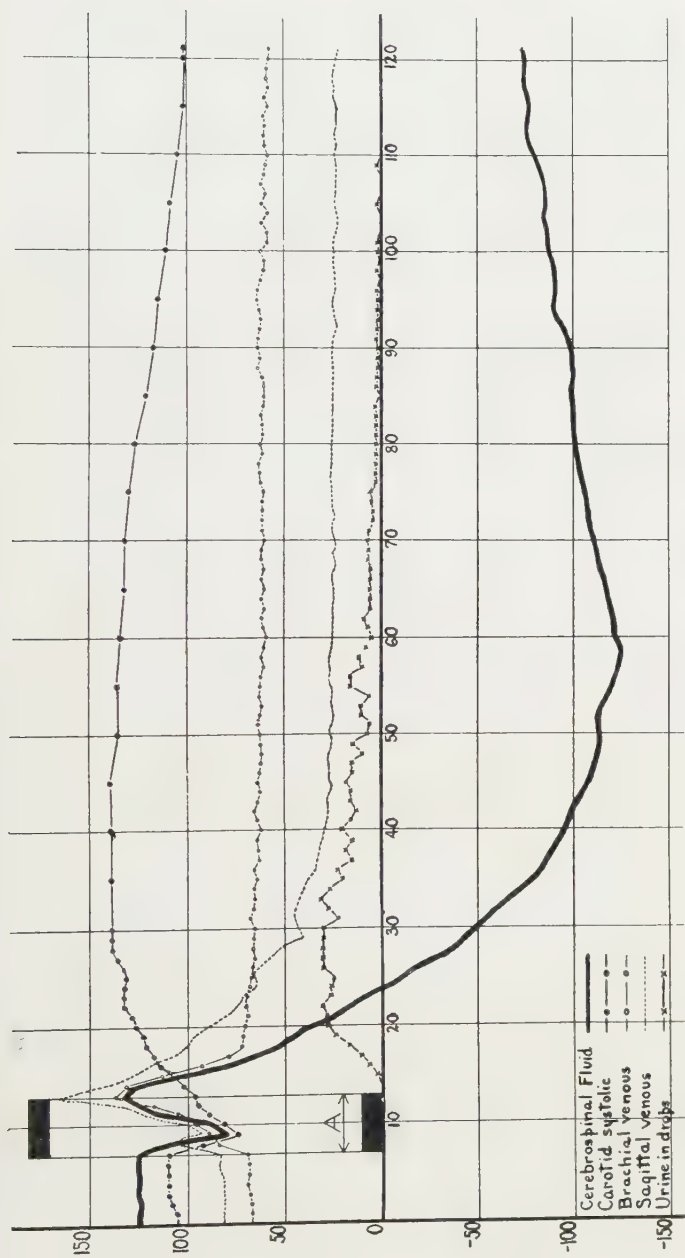


FIG. 2. Dog (experiment 97). Ordinates represent millimeters of Ringer's solution or mercury (carotid pressure); abscissae represent time in minutes. During interval A, intravenous injection of 30 cc. of 30 per cent solution of sodium chloride. Cerebrospinal fluid pressure obtained from occipito-atlantoid manometer; animal in horizontal position.

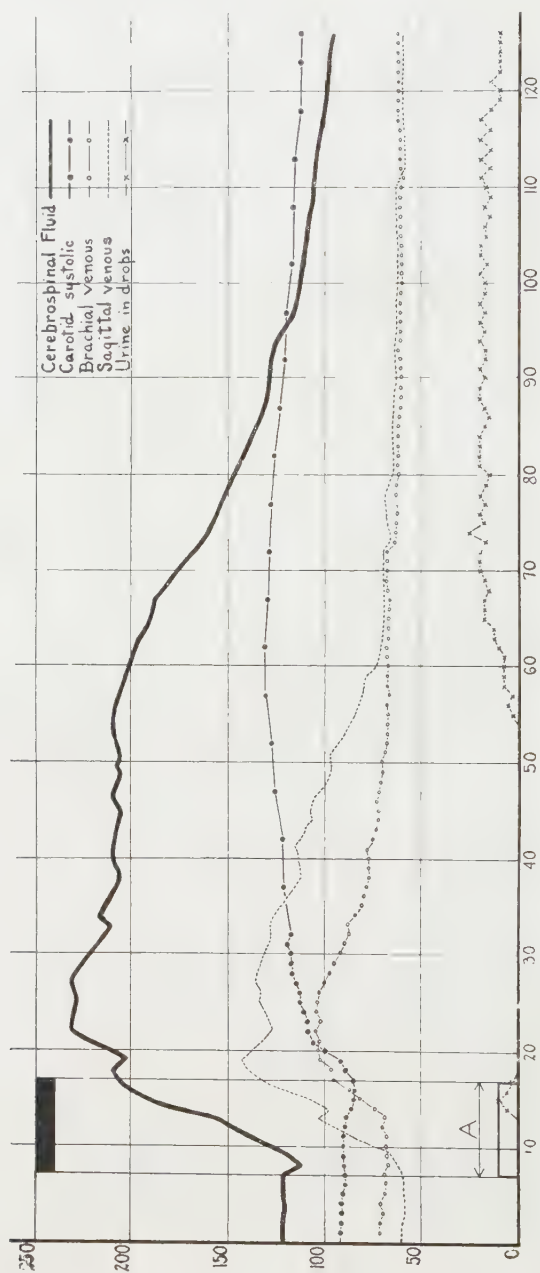


FIG. 3. Dog (experiment 109). Ordinates represent millimeters of Ringer's solution or mercury (carotid pressure); abscissae represent time in minutes. During interval A, intravenous injection of 150 cc. of distilled water. Cerebrospinal fluid pressure obtained from occipito-atlantoid manometer; animal in horizontal position.

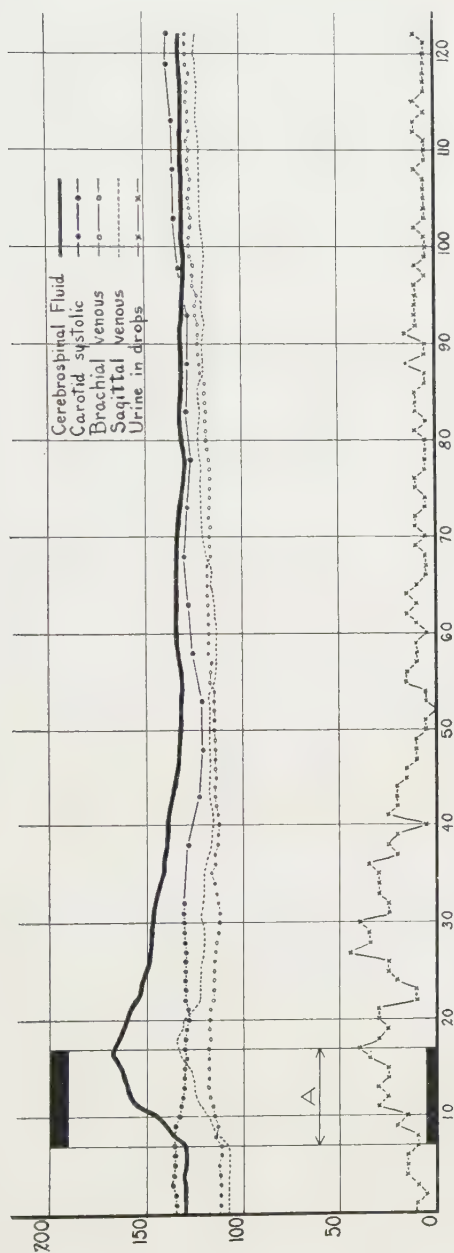


FIG. 4. Dog (experiment 112). Ordinates represent millimeters of Ringer's solution or mercury (carotid pressure); abscissae represent time in minutes. During interval A, intravenous injection of 150 cc. of Ringer's solution. Cerebrospinal fluid pressure obtained from occipito-atlantoid manometer; animal in horizontal position.

existed during the period of injection and quickly subsided thereafter (fig. 4). These findings of McKibben and the writer have been confirmed in numerous experimental and clinical investigations (Cushing and Foley (17), Foley and Putnam (16), Sachs and Belcher (28), Ebaugh and Stevenson (11), Wachs and Malone (29), Foley (15), Dowman (10), Fay (14), Leriche and Wertheimer (23), Hughson (19), Howe (18), and others).

Associated with these marked changes in the pressure of the cerebrospinal fluid were equally marked changes in the volume of the brain (Weed and McKibben (41)). The intravenous injection of the strongly hypertonic solution produced a greatly shrunken brain, particularly marked in an animal whose calvarium had been trephined and dura opened. Conversely, the hypotonic solution on intravenous injection caused an outspoken swelling of the brain, easily demonstrated by herniation of the brain substance through any cranial and dural openings. Ringer's solution, under similar condition, caused no appreciable change in the volume of the brain.

The explanation for the experimental modification of the pressure of the cerebrospinal fluid under such conditions seems fairly simple, being related to change in the osmotic pressure of the blood. With the intravenous injection of a strongly hypertonic solution, the osmotic pressure of the blood is acutely increased. This increase in the osmotic pressure of the blood results in the attraction of water from all of the tissues and fluid reservoirs of the body: the brain and cerebrospinal fluid seem to afford a reservoir from which fluid may be easily withdrawn by the increased salt concentration of the blood. During the process of fluid-extraction by the blood stream, salts are probably passed from blood-stream into the tissues (brain and possibly the cerebrospinal fluid). On the other hand, the intravenous injection of a large quantity of hypotonic solution lowers the osmotic pressure of the blood and attracts salts from all of the body tissues, simultaneously passing a large quantity of water from the blood-stream into the body tissues and fluids. And here again the brain and the cerebrospinal fluid seem to offer opportunities for the easy transmission of water from the blood-stream.

With Hughson, the writer (39) carried these primary observations some steps farther, taking records of the pressures of the cerebral arteries and veins, as well as of the cerebrospinal fluid. In these observations it was shown that the alterations in pressure of cere-

brospinal fluid, effected by the intravenous injection of solutions of various concentrations, are in large part independent of the alterations in the intracranial arterial and venous pressures. The relationship between the pressure of the cerebrospinal fluid and that of the superior sagittal sinus (fig. 1) found under normal conditions (cerebrospinal fluid pressure exceeding that of the cerebral veins) held during the alterations in pressures caused by the intravenous injection of hypotonic and isotonic solutions (figs. 3 and 4). On the other hand, after the intravenous injection of strongly hypertonic solutions, the pressure relationships were reversed (fig. 2); here the pressure in the superior sagittal sinus always exceeded that in the cerebrospinal fluid during the period of physiological effect. In these experiments also, certain other generalizations, already presented in the discussion of the relationship of the normal pressure of the cerebrospinal fluid to that in the cerebral veins and arteries, were ascertained.

The situation then in regard to experimental alteration of the pressure of the cerebrospinal fluid is by no means as satisfactory as is the situation with regard to other phases of recent work. With the exception of studies of the effect of intravenous injections of various concentrations, no consideration has been given to the experimental alteration of the volume of the brain, and until regard is placed upon this factor, the effect of drugs, chemicals, and tissue extracts upon the rate of production of cerebrospinal fluid cannot be ascertained with any exactness.

BONY CONTAINERS OF THE CENTRAL NERVOUS SYSTEM

The pressure of the cerebrospinal fluid, relatively independent as it may be, can hardly be discussed without taking account of the bony containers of the central nervous system. This statement brings immediately before one the question of the truth or untruth of the thesis which has become known as the Monro-Kellie doctrine. This doctrine relates primarily to consideration of the bony containers of the central nervous system (skull and vertebral column) as a rigid box, so that the central nervous system is removed from all external pressures and subject only to internal pressures such as are brought to it through the blood-stream or are created by the activities of its own particular set of cells. It will serve to elucidate the problem if the Monro-Kellie thesis is considered in some detail.

In 1783, Alexander Monro the younger (26) presented the hypoth-

esis that the quantity of blood circulating within the bony coverings of the central nervous system is at all times constant. This conception necessarily involved the assumption that the substance of the brain, like that of other solids of the body, is nearly incompressible and is "enclosed in a case of bone," assuring therefore constancy of the blood content. Monro's thesis was developed by Kellie (20), who forty years later carried out supposedly critical investigations of the quantity of blood existing within the cerebral vessels of animals and men. Kellie reached the conclusion that in the intact condition of the cranium the quantity of blood could not be altered, but if the animal be trephined the intracranial blood could largely be removed by hemorrhage. Many clinical investigations followed Kellie's publication in 1824: the Monro-Kellie doctrine received wide acceptance.

This hypothesis was of course evolved before knowledge of the cerebrospinal fluid became general, and with increased information regarding the fluid derived from Magendie's studies (25), modification of the doctrine became quickly necessary. Burrows (5) was apparently the first investigator to bring the cerebrospinal fluid into consideration as one of the intracranial elements. Burrows placed but little emphasis on the thesis that the intracranial blood volume was at all times constant, for he felt that any vacated space in the cranium could be replaced by "extravascular serum" (cerebrospinal fluid) or "resiliency of the cerebral substance under diminished pressure." He admitted that "the whole contents of the cranium, that is, the brain, the blood and this serum (cerebrospinal fluid) together, must be at all times nearly a constant quantity."

Many physiologists in the next forty years subjected this hypothesis of a constant intracranial volume of blood to experimental tests and came to different conclusions regarding the accuracy of the assumption. Kussmaul and Tenner (22) and also Donders (9) attempted, by direct observation through a cranial window, to secure evidence regarding the intracranial vascular volume; their observations, while more reliable than those made upon dead animals, did not permit control of all of the necessary factors. Hill, using more refined methods of determination, concluded that "the volume of blood in the brain is in all physiological conditions but slightly variable." Dixon and Halliburton (8), twenty years after Hill, studied the general problems of the Monro-Kellie thesis in a somewhat different way and were able to show great variation in the intracranial pressures and in the rela-

tions of the cerebrospinal fluid pressure to that in the torcular Herophili. Their assertion that (p. 153) "the cranial contents cannot any longer be regarded as a fixed quantity without the power of expanding or contracting in volume" necessarily involved somewhat extreme modification of the whole doctrine. Their findings established the fact that variations in the pressure of the cerebrospinal fluid and in the cerebral venous system could be effected without the exact correspondence in pressure-relationships given by Hill.

This, then, was the status of the problem when the writer demonstrated with McKibben (41) that alterations in the volume of the brain could be effected experimentally. For as recorded in the foregoing section of this communication, it was shown that the intravenous injection of a strongly hypertonic solution produced a greatly shrunken brain; similar injection of a hypotonic solution, a swollen brain, while intravenous injection of large quantities of isotonic solution had no appreciable effect on brain volume. These changes in the volume of the brain under experimental conditions necessarily involved modification of the Monro-Kellie doctrine and the conclusion (Weed and McKibben (41)) was drawn that (p. 553) "the cranial cavity is relatively fixed in volume and is completely filled by brain, cerebrospinal fluid and blood; variations in any one of the three elements may occur, compensation being afforded by alteration in the volume of one or both of the remaining elements." This idea, which was somewhat similar to that advanced by Burrows, was based largely on an anatomical explanation of the production of negative pressures of the cerebrospinal fluid by the intravenous injection of strongly hypertonic solutions. The occurrence of negative pressures of the cerebrospinal fluid under these experimental conditions suggested strongly that the cranium was within the tested physiological limits a "closed box" while the experimental alteration of brain volume introduced the conception that the volume of the brain was not absolutely fixed but that within narrow limits physiological variations in its bulk occurred.

Following this publication, Becht (2) accepted the hypothesis of the cranium as a closed cavity and stated one aspect of the doctrine as follows (p. 12):

It is well known that both brain and cord, because of their large water content are practically incompressible; because of its bony structure the skull and neural canal are nearly undilatable to pressure except at the membranes covering the foramina between the vertebrae. To the same degree that the brain is incompress-

sible and the skull undilatable by pressure are they lacking in elastic recoil when the pressure is removed

Taking these investigations as a whole it is apparent that the *Monro-Kellie* doctrine of fixed intracranial contents has been largely accepted by workers in the field though it has been modified at times to meet requirements of later knowledge. But it seems clear that practically none of the workers has determined accurately the anatomical mechanism which constitutes the closed rigid system, though physiological hypotheses have been largely developed upon its acceptance. *Kellie* (20) really subjected the conception to experimentation and his account of the recession of the brain from the skull in an animal which had been trephined (*dura* opened ?) marked the initial demonstration of the function of the intact skull in intracranial relationships. *Ecker* (12) also observed in a trephined animal a marked diminution in the size of the brain when the carotid arteries were divided. Such observations, in contrast to the findings in animals with intact cranial cavities, gave indication of this function of the closed cranium as a factor in the maintenance of the pressure relationships about the central nervous system.

In order to ascertain the essential truth or untruth of the *Monro-Kellie* doctrine, *Hughson* and the writer (38) some years ago undertook experiments which promised to give a better conception of the mechanism than existed. The strongest argument in favor of the thesis that the central nervous system was enclosed in a rigid container seemed to lie in the production of negative pressures of extreme degrees within the cranial cavity. For if the central nervous system were not contained within a rigid system negative pressures could hardly be obtained. It was known that anatomically the cranium possesses on gross inspection the accepted character of a rigid container with the *dura* everywhere tightly applied to the inner surface of the skull. And the *dura*, because of its inelastic character was considered to be a rigid barrier against expansion outwards, but unless held in place it could not in any way function as a membrane to resist atmospheric pressure from without. In the spinal region the similarity of the bony coverings of the central nervous system to this closed box is by no means so simple of explanation. Although the vertebral bodies and arches form a rigid channel, bridging the segmental ligaments, the *dura mater* does not adhere to the inner surface of these bony arches. The intervening epidural space is in the mammals com-

posed of a loose, fatty areolar tissue, containing an extensive plexus of thin-walled veins. These anatomical structures in the subdural space do not possess sufficient fibrous bundles to constitute a satisfactory connection with the vertebrae: the question immediately is presented as to whether on evacuation of the spinal dural contents the dura would remain in position, due to the bridgework of fibrous tissues and to the creation of a partial vacuum in the epidural tissue, or whether stretching of the fibrous tissues and dilatation of the veins would permit collapse of the dura. In the latter case the vertebral channel could not be assumed to function as a closed box for the central nervous system. And in the occipito-atlantoid ligament which possesses sufficient elasticity to permit transmission of the pulsations of the cerebrospinal fluid, there exists another anatomical structure lacking rigidity.

With these questions before them, Hughson and the writer (38) devised two experiments which seemed to afford insight into the integrity of the bony coverings of the central nervous system as constituting a closed box within tested physiological limits. In the first type of experiment, the bony calvarium on one side was widely removed, without interfering with the intact character of the dura mater. With the pachymeninx exposed to atmospheric pressure, an experimental set-up was had which permitted obtaining the pressure of the cerebrospinal fluid in the customary way, for the positive pressure of the cerebrospinal fluid kept the dura expanded. On the other hand, on removal of the bony covering, the dura mater could collapse inward if the internal pressure of the central nervous system were reduced or removed. With this set-up and with the measurement of the pressure of the cerebrospinal fluid, repeated injections of a strongly hypertonic solution were given to young animals. These injections far exceeded in quantity the amounts necessary for the invariable production of negative cerebrospinal fluid pressures in animals of similar size and age with intact crania. In these trephined animals, however, under no circumstances, even with injection of the hypertonic solution in such amount as finally to kill the animal, was a negative pressure ever observed (fig. 5). In almost every case the repeated injection reduced the pressure of the cerebrospinal fluid to approximately 18 mm. of fluid. This positive pressure of 18 mm. represented the hydrostatic height of one cerebral hemisphere above the occipito-atlantoid needle with the animal reclining on its side. This type of experiment

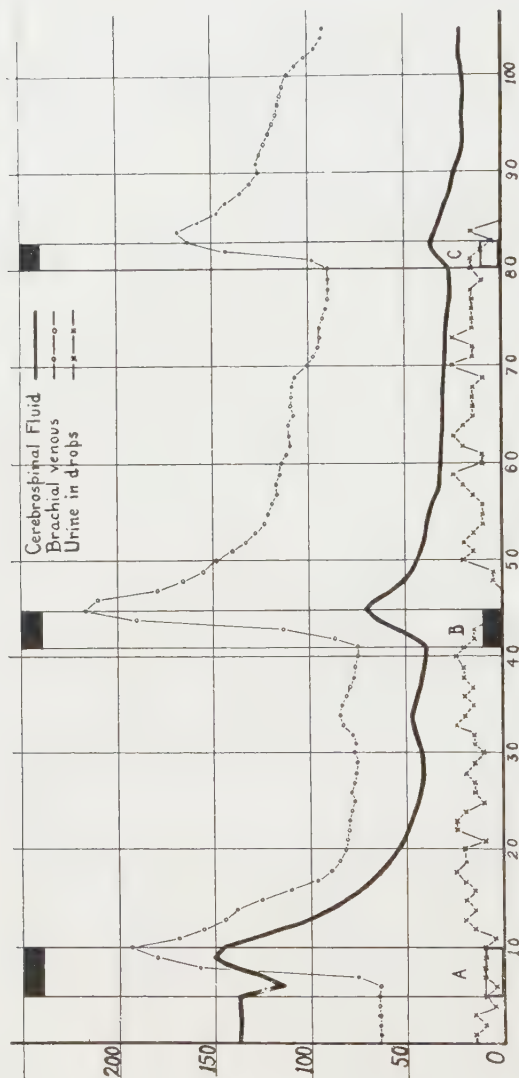


FIG. 5. Cat (experiment 89). Ordinates represent millimeters of Ringer's solution; abscissae represent time in minutes. During interval A, intravenous injection of 10 cc. of 30 per cent solution of sodium chloride; during interval B, intravenous injection of 8 cc. of same solution; during interval C, intravenous injection of 5 cc. of same solution. Right half of calvarium removed, with intact dura exposed to atmospheric pressure. Cerebrospinal fluid pressure obtained by occipito-atlantoid manometer; animal in horizontal position.

then demonstrated that negative pressures of the cerebrospinal fluid could not be obtained when the integrity of the bony calvarium on one side was destroyed.

The second type of experiment gave even more striking results in favor of the same thesis. The experimental procedure was so devised

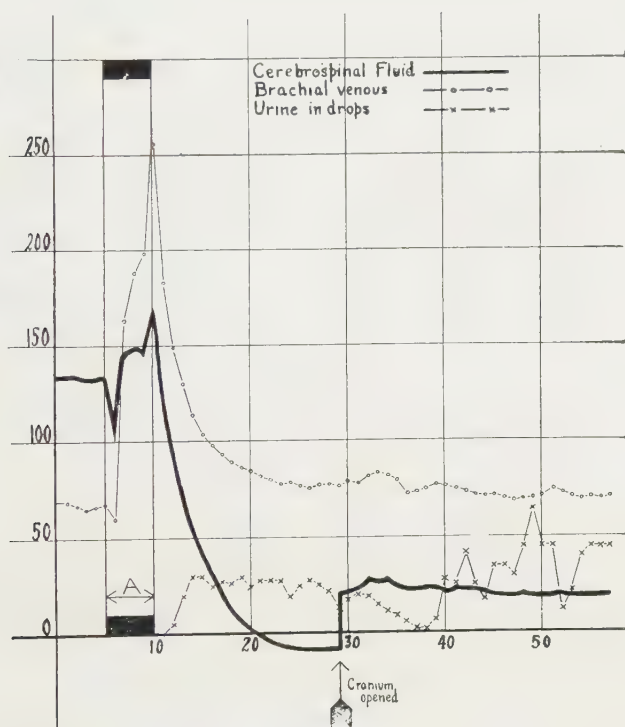


FIG. 6. Cat (experiment 52). Ordinates represent millimeters of Ringer's solution; abscissae represent time in minutes. During interval A, intravenous injection of 10 cc. of 30 per cent solution of sodium chloride. Cranium opened and subsequently sealed. Cerebrospinal fluid pressure by occipito-atlantoid manometer; animal in horizontal position.

as to afford an opening into the temporal region of the skull, without injury to the dura, with later closure of this opening by a glass slide sealed with heavy vaseline. The experiment was simply carried out: after reflecting the skin and temporal muscle, a trephine opening was made in the temporal bone and the opening enlarged by rongeurs.

Leaving the dura intact, the hole was sealed with vaseline and the glass slide applied. In this way the dura mater acted as an inelastic membrane preventing expansion of the brain outward; the glass slide with the sealing mechanism prevented collapse of the dura due to atmospheric pressure. As soon as this part of the experimental procedure was complete, an occipito-atlantoid puncture was made in the animal and the needle connected in the customary way to a "U" manometer.

After the initial period for control readings, an intravenous injection of a strongly hypertonic solution (30 per cent NaCl) was given to the animal. The dose of sodium chloride was large enough in every case to reduce the pressure of the cerebrospinal fluid to negative values. At the time when the pressure of this fluid was below zero, the glass slide was removed, thus subjecting the dura mater immediately to atmospheric pressure. As a result of this, the pressure of the cerebrospinal fluid immediately rose from its negative value to a positive reading of approximately 18 mm. (fig. 6). This positive value again represented the height of one cerebral hemisphere above the puncture needle, with the animal lying on its side. The sudden transition of the pressure of the cerebrospinal fluid from below zero to a positive level indicated that the intactness of the bony vault of the skull was essential for the maintenance of the closed box character of the bony coverings of the central nervous system.

It is obvious then that the Monro-Kellie doctrine of a closed box system containing the central nervous system is essentially correct. While the original doctrine must be modified in some ways to meet more recent advances in our knowledge, the modifications are slight, involving merely the idea of variability in the quantity of the circulating blood and of the cerebrospinal fluid and in the volume of the brain. The total contents of the cranium must at all times be approximately equal. Variations in any one of the three elements—brain, blood and cerebrospinal fluid—may occur, but variation in volume of any one of the three is immediately compensated for by reciprocal variations in one or both of the remaining elements.

EFFECT OF POSTURE ON THE PRESSURE OF CEREBROSPINAL FLUID

With the exception of experimental studies by Leonard Hill (17), surprisingly little regard has been paid to the effect of posture on the pressure of the cerebrospinal fluid. Certain clinical observations of pressure, taken in human beings in the recumbent and in the rela-

tively up-right position (Barré and Schrapf (1), Zylberlast-Zand (43), have indicated that posture plays a rôle in the exact level of pressure recorded. All of these observations have been of great interest but they have merely indicated the supreme importance of additional studies with adequate experimental control. Leonard Hill's conclusions were largely of the nature of hypothetical deductions from a few observations, but unquestionably Leonard Hill should be given credit for the introduction of the idea that the pressure of the cerebrospinal fluid is altered markedly by changes in posture. Leonard Hill stated that the pressure in the human being might be anything from zero to 50 mm. Hg., depending on whether the subject of measurement was in the up-right or recumbent position.

All of the recent adequately controlled experimental studies of the pressure of the cerebrospinal fluid have been based on four-footed laboratory mammals lying in horizontal positions during the period of observation. These studies, while giving for the first time an exact idea of the relationships existing between the pressure of the cerebrospinal fluid and that in the cerebral arteries and veins, are necessarily limited in affording bases for generalizations regarding the pressure of the fluid under all conditions of animal life. It must, however, be granted that the normal body-position for the common laboratory mammals is a horizontal rather than a vertical one, such as exists in man.

During the past year the writer has studied the effect of posture on the pressure of the cerebrospinal fluid in cats and dogs. The technical difficulties of securing records of the pressure of the cerebrospinal fluid alone are not great even though the animal be rotated through 180 degrees, but it proved for some time difficult to secure accurate simultaneous records of the pressures existing in the superior sagittal sinus, in the brachial vein, and in the carotid artery, thus affording adequate physiological control. After several futile attempts, the writer was able to devise a tilting table, to which the experimental animal could be securely attached. Pressures of the cerebrospinal fluid were obtained at thirty-second or one-minute intervals by attaching a U-shaped or straight manometer of 1 mm. bore to a puncture needle in the occipito-atlantoid ligament, or in the lumbar region. Carotid pressure was obtained in the usual manner by a mercury manometer. The brachial venous pressure was secured by means of the insertion of suitable cannula in the superficial brachial vein and

connection of this cannula to a manometer containing salt solution. From a reservoir small amounts of salt solution were introduced into the brachial vein, thus giving accurate readings at thirty-second or one-minute intervals. The pressure in the superior sagittal sinus was obtained by the method of Weed and Hughson (39), the connection between manometer and puncture needle being modified so that the animal could be tilted.

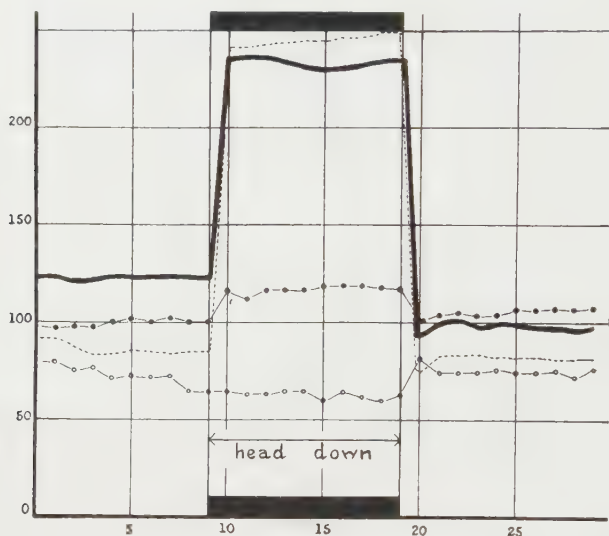


FIG. 7. Dog (experiment A18). Ordinates represent millimeters of Ringer's solution or mercury (carotid pressure); abscissae represent time in minutes. Cerebrospinal fluid pressure from occipito-atlantoid manometer represented by solid black line; sagittal venous pressure by interrupted line; brachial venous pressure, by rings and dashes; carotid arterial pressure, by solid circles and dashes. Animal in horizontal position except during interval marked by solid block, during which animal was shifted to vertical head-down position.

The first series of experiments were all carried out in such a way that the animal could be suddenly tilted from a horizontal to a vertical position, with head down and tail up. During the process of tilting, (and the time of tilting to 90 degrees occupied approximately ten seconds) certain readjustments in the levels of cannulae had to be made; but after some experience these adjustments could be quickly and accurately effected. The animals were all subjected to ether

anesthesia, without preliminary preparation that day except withholding of food. The anesthesia was initially administered by cone, and as soon as possible connection of the animal to a Woulfe bottle, through a suitable tracheal tube, was made. When all of the instruments were properly recording so that observations could be made continuously, a control period of five or ten minutes was taken. In these control periods, as in figure 7, the pressure of the cerebrospinal fluid was customarily in the neighborhood of 125 mm. of fluid, while that in the superior sagittal sinus was somewhat lower. The carotid arterial pressure was in the usual experiment 100 to 120 mm. Hg., while the brachial venous pressure varied considerably from animal to animal but was usually under 100 mm. of salt solution.

To avoid great complexity in the findings, it is probably better to discuss first the alterations in pressure of the cerebrospinal fluid, as obtained by occipito-atlantoid puncture. In numerous experiments, the initial pressure of the cerebrospinal fluid was in the neighborhood of 125 mm. and during the control period almost no fluctuation in this pressure occurred. On tilting the animal abruptly to a vertical position, with head down, the pressure of the cerebrospinal fluid rose very rapidly, usually 80 to 110 mm. of fluid, thus reaching levels in the neighborhood of 230 mm. (fig. 7). In 39 different observations, the increase in cerebrospinal fluid pressure averaged 103.3 mm. of fluid. In this vertical position, the heightened level was maintained with but slight alteration. When the animal was brought down to the horizontal position, the pressure of the cerebrospinal fluid abruptly fell, usually to a level slightly below that initially held (fig. 7). The reduction in pressure from the initial horizontal reading was customarily not over 20 mm. (average in 39 observations, 14.9 mm.), though occasionally greater differences were noted in those cases in which the animal was maintained in the vertical position for a long period (ten minutes or over).

Entirely different pressure alterations occurred when the pressure of the cerebrospinal fluid was taken by lumbar puncture rather than by occipito-atlantoid puncture. In one animal, for instance (fig. 8), the initial pressure of the cerebrospinal fluid, as determined by lumbar puncture, ranged during the control period from 170 to 160 mm. On being tilted up-right, with head down, the lumbar pressure fell to plus 5 mm., and after five minutes in this position the animal was restored to the recumbent posture. The lumbar pressure then rose to

130 mm., and during the next fifteen minutes was maintained at approximately that level.

In another series, simultaneous records of occipito-atlantoid and lumbar pressures of the cerebrospinal fluid were taken, and the animals again tilted vertically, with heads down. Under these conditions, marked alterations in the two pressures occurred. In one animal in the horizontal position, lumbar and occipito-atlantoid pressures of the cerebrospinal fluid during a control period were identical, at 120 to 125 mm. of fluid. On being tilted up-right (head down), the occi-

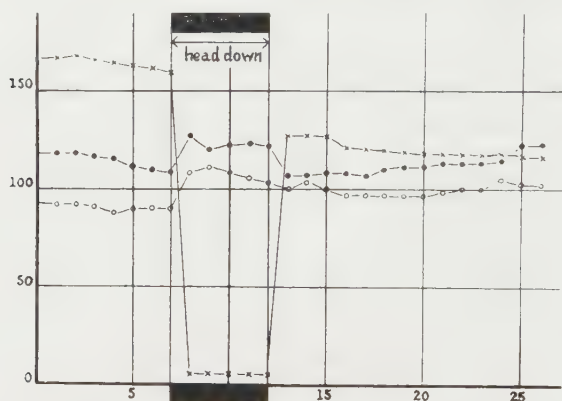


FIG. 8. Dog (experiment A9). Ordinates represent millimeters of Ringer's solution or mercury (carotid pressure); abscissae represent time in minutes. Cerebrospinal fluid pressure from lumbar manometer represented by crosses and dashes; brachial venous pressure, by rings and dashes; carotid arterial pressure, by solid circles and dashes. Animal in horizontal position except during interval marked by solid block, during which animal was shifted to vertical head-down position.

pito-atlantoid pressure rose to 240 mm., while the lumbar pressure fell to minus 100 mm. With the animal in this vertical position, the lumbar and the occipito-atlantoid manometers were parallel in the same vertical plane, side by side. It could be seen that the fluid in the two manometers occupied exactly the same level, although under the experimental conditions the reading in the occipito-atlantoid manometer was positive, while in the lumbar needle it was negative. On restoring the animal to the horizontal position, both of these pressures came to rest at approximately the same level, slightly in excess of 100 mm.

Alterations in the other pressures recorded occur during these extreme postural readjustments. A typical experiment may be given to show these pressure changes. In figure 7, based on the findings in a young male dog, the pressure of the cerebrospinal fluid during the control period was constant at 125 mm. This pressure rose abruptly on change to the vertical position to 235 mm. and remained very stable at that level. The sagittal pressure in the control period was constant at 90 to 85 mm. On tilting to the up-right, this venous pressure rose abruptly to 241 mm., and then mounted slowly to 250 mm. With restoration of the horizontal position, the sagittal venous pressure fell to 85 mm., while the cerebrospinal fluid pressure became constant at approximately 100 mm. During the control period, the carotid pressure was 100 mm. Hg.; this rose to 115 mm. immediately after tilting to the up-right and then remained at this level throughout the period of vertical posture. On resuming the horizontal position the pressure fell 15 mm. and then rose slightly. The brachial venous pressure, which during the control period was constant between 75 and 65 mm., showed no significant change during the up-right position, but on resumption of the horizontal position, mounted slightly. In other experiments, the alterations in pressures were equally abrupt, but these alterations were almost entirely in the sagittal venous and in the cerebrospinal fluid pressures, the carotid arterial and the brachial venous pressures showing no significant changes. The sagittal venous pressure, which during the control period in all experiments was less than the pressure of the cerebrospinal fluid, frequently exceeded in the vertical head-down position the pressure of cerebrospinal fluid. In other cases the sagittal venous pressures remained below the pressures in the subarachnoid space (fig. 9), but the increase in sagittal pressure always exceeded the increase in cerebrospinal fluid. The average increase in sagittal pressure in a large series of experiments was 172.7 mm.—an increase to be compared directly with the average increase of 103.3 mm. in the pressure of the cerebrospinal fluid.

The pressure-alterations in the cerebrospinal fluid are almost as marked in tilting from the horizontal to a vertical tail-down position as to the vertical head-down position. In figures 9 and 10 the reductions in the pressure of the cerebrospinal fluid, determined by occipito-atlantoid manometer, are graphically shown. Customarily the reduction in occipito-atlantoid pressure is from 70 to 100 mm., the

average reduction of pressure being in this series 81.1 mm. No significant change in either carotid arterial or brachial venous pressure occurred during this tilting from the horizontal to the vertical tail-down position, but the sagittal venous pressure showed tremendous reduction (fig. 9). In the series, the average reduction of sagittal venous pressure was 101.8 mm.—a figure which may be compared directly with the average reduction of 81.1 mm. in the pressure of the occipital cerebrospinal fluid in the same group of animals.

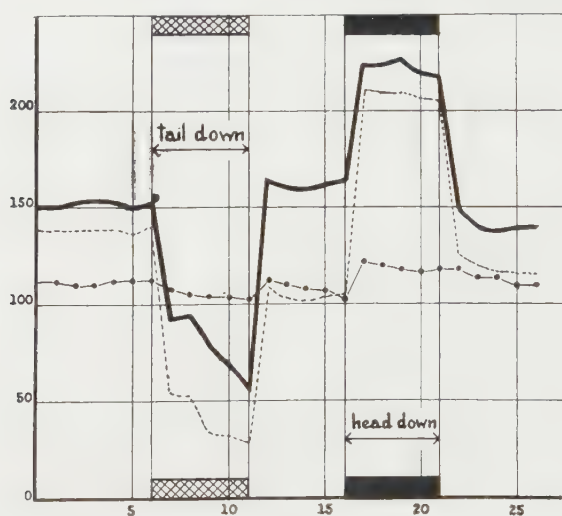


FIG. 9. Dog (experiment A24). Ordinates represent millimeters of Ringer's solution or mercury (carotid pressure); abscissae represent time in minutes. Cerebrospinal fluid pressure from occipito-atlantoid manometer represented by solid black line; sagittal venous pressure, by interrupted line; carotid arterial pressure, by solid circles and dashes. Animal in horizontal position except during interval marked by diagonal cross-hatching, during which animal was shifted to vertical, tail-down position; and during intervals marked by solid block during which animal was shifted to vertical, head-down position.

In addition to these pressure-reductions shown in the postural change from the horizontal to the vertical tail-down position, there are other phenomena to be noted in this group of experiments. Most important is the restoration of the occipital cerebrospinal fluid pressures on return to the horizontal to levels slightly in excess of those held during the initial control periods (figs. 9 and 10). In most cases this

excess pressure was obliterated within a few minutes after return of the animal to the horizontal, and levels practically identical with those existing in the control period were maintained, though occasionally divergencies of small extent occurred.

Quite similar to these results are the pressure-changes brought about by abrupt shifts from the vertical head-down position to the

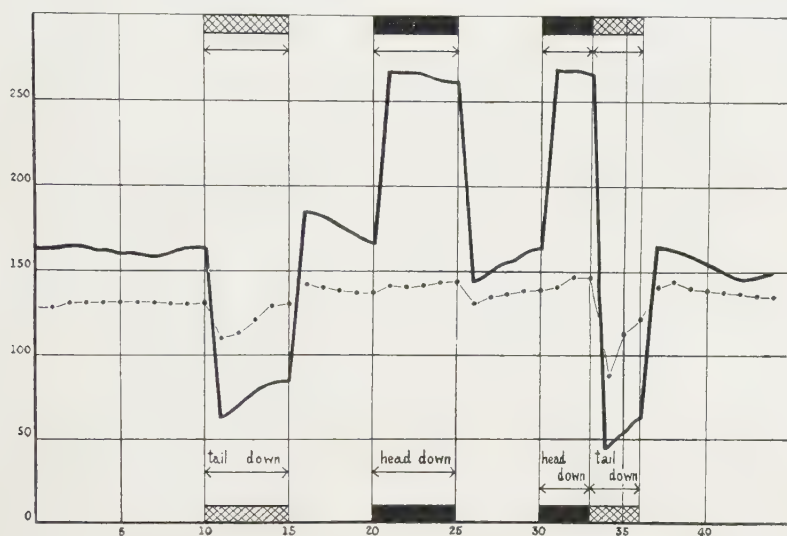


FIG. 10. Dog (experiment A21). Ordinates represent millimeters of Ringer's solution or mercury (carotid pressure); abscissae represent time in minutes. Cerebrospinal fluid pressure from occipito-atlantoid manometer represented by solid black line; carotid arterial pressure, by solid circles and dashes. Animal in horizontal position except during intervals marked by diagonal cross-hatching during which animal was shifted to vertical tail-down position; and during intervals marked by solid block during which animal was shifted to vertical, head-down position.

vertical tail-down position. In figure 10, these alterations in pressures are recorded for the cerebrospinal fluid (as obtained by occipito-atlantoid needle), and for the carotid artery. The alterations in each of these pressures, effected by the rapid rotation of the animal through 180 degrees, are directly comparable to the 90 degree shifts in position shown in the first part of the graph. The pressure-changes all occurred in the short interval necessary for the mechanical change in the position of the animal.

It should be noted that animals, even though deeply anesthetized, were relatively easily fatigued by these abrupt changes from horizontal to vertical positions. Many times spontaneous respirations ceased; at other times, vasomotor collapse seemed to occur. Some animals

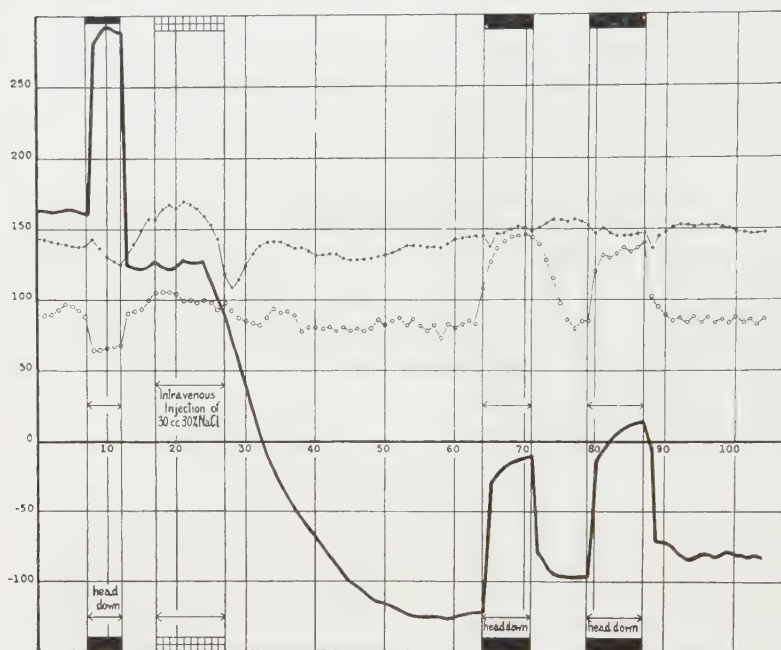


FIG. 11. Dog (experiment A15). Ordinates represent millimeters of Ringer's solution or mercury (carotid pressure); abscissae represent time in minutes. Cerebrospinal fluid pressure from occipito-atlantoid manometer represented by solid black line; brachial venous pressure, by rings and dashes; carotid arterial pressure, by solid circles and dashes. During interval marked by rectangular cross-hatching, intravenous injection of 30 cc. of 30 per cent solution of sodium chloride. Animal in horizontal position except during intervals marked by solid block, in which animal was shifted to vertical, head-down position.

however appeared to stand these abrupt changes in posture quite well and showed no apparent fatigue in the reaction even though they were tilted five or six times in the course of an experiment.

In an attempt to ascertain what relation, if any, the size of the spinal subarachnoid space has to the changes of pressure in the cere-

brospinal fluid, a small series of observations was undertaken. In these, the size of the spinal and cerebral subarachnoid spaces was altered by intravenous injections of strongly hypertonic (30 per cent NaCl) and hypotonic (distilled water) solutions. With the hypertonic injection the central nervous system was markedly shrunk, thus increasing the size of the subarachnoid space while after the

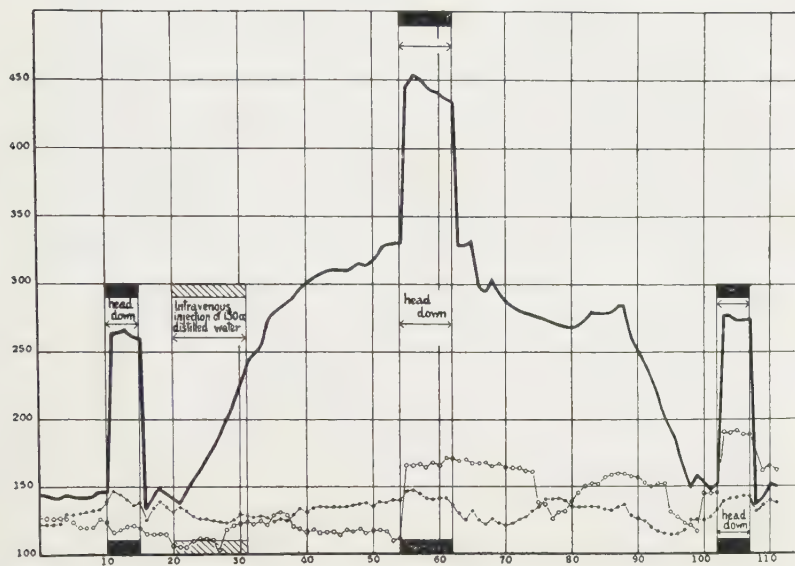


FIG. 12. Dog (experiment A16). Ordinates represent millimeters of Ringer's solution or mercury (carotid pressure); abscissae represent time in minutes. Cerebrospinal fluid pressure from occipito-atlantoid manometer represented by solid black line; brachial venous pressure, by rings and dashes; carotid arterial pressure, by solid circles and dashes. During interval marked by diagonal hatching, intravenous injection of 150 cc. of distilled water. Animal in horizontal position except during intervals marked by solid block in which animal was shifted to vertical, head-down position.

hypotonic injection the subarachnoid space was diminished in size due to the swelling of the nervous tissue. In figure 11, the results of tilting the animal from the horizontal to the vertical head-down position are shown, both before and after the intravenous injection of the hypertonic solution. The initial tilting resulted in an increase in occipital cerebrospinal fluid pressure of 132 mm. (from 163 mm. to

295 mm.), while after extreme reduction of the fluid pressure due to the hypertonic solution, tilting in the same way increased the pressure 111 mm. (from minus 121 mm. to minus 10 mm.), and again 107 mm. (from minus 95 mm. to plus 12 mm.). These results show that increase in the size of the subarachnoid space does not in any way change the magnitude of the pressure-alteration after tilting through 90 degrees; the pressure-changes are of approximately the same extent before and after the injection.

Conversely, the same general phenomenon was observed after the intravenous injection of the hypotonic solution. In the experiment on which figure 12 is based, the change from the horizontal to the vertical head-down position caused an increase of occipital cerebrospinal fluid pressure of 118 mm. (from 147 mm. to 265 mm.). After the pressure of the occipital cerebrospinal fluid had risen to 330 mm. in the horizontal position due to the injection of water, the same tilting increased the pressure by 125 mm., and later, when the cerebrospinal fluid had returned to normal readings, tilting caused an increase of 125 mm. These increases in the pressure of the fluid, due to tilting to the vertical, are all of the same magnitude: decrease in the caliber of the subarachnoid space may be considered therefore to be without effect on the pressure-alterations in the cerebrospinal fluid as effected by changes in posture of the experimental animal.

With these findings before one, it becomes interesting to speculate about the general mechanisms or pressure-changes in the central nervous system on postural readjustments. First, it should be pointed out that in all experiments measurement of the distance between the occipital protuberance and last lumbar spine was made. In the series reported, with employment of young rather small dogs, this distance was found to be slightly in excess of 400 mm. Realizing that the cerebrospinal fluid occupies at least this space, then with the animal in the vertical positions (head-down or tail-down) account must be taken of the effect of this hydrostatic column of fluid above or below the occipito-atlantoid needle. In the change from horizontal to the vertical head-down position, the occipital cerebrospinal fluid pressure rose 103.3 mm. as an average, while in the change from horizontal to tail-down position the fall was 81.1 mm. These pressure changes of 103.3 mm. and 81.1 mm. should therefore be directly referred to the hydrostatic column of 400 mm. of fluid. It thus becomes obvious that the entire hydrostatic pressure, theoretically possible in the

vertical position, is not superimposed upon the normal positive pressure (about 130 mm.) existing in the horizontal position. The increased pressure of approximately 200 mm. noted clinically (Barré and Schrapf (1), Zylberlast-Zand (43), when lumbar pressures are taken in the vertical instead of in the prone position are comparable

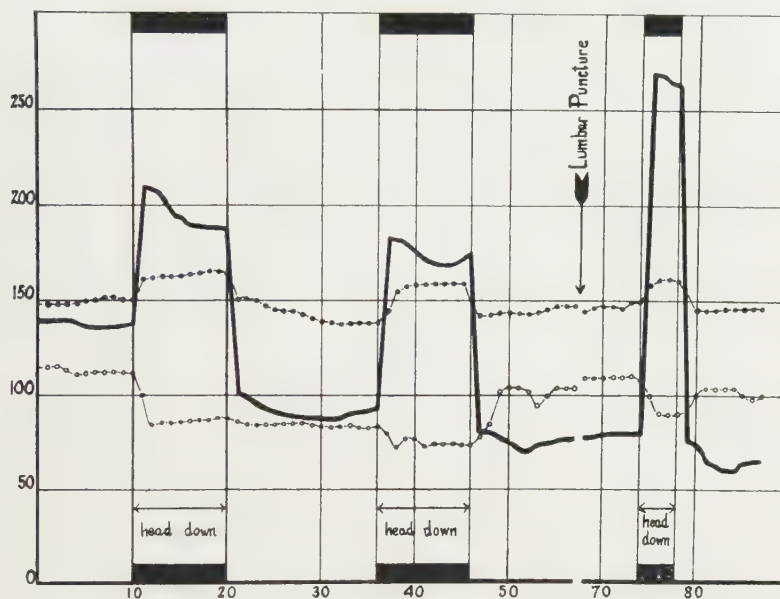


FIG. 13. Dog (experiment A3). Ordinates represent millimeters of Ringer's solution or mercury (carotid pressure); abscissae represent time in minutes. Cerebrospinal fluid pressure from occipito-atlantoid manometer represented by solid black line; brachial venous pressure, by rings and dashes; carotid arterial pressure by solid circles and dashes. Animal in horizontal position except during intervals marked by solid blocks in which animal was shifted to vertical, head-down position. During interval, fifty-seven to sixty-eight minutes, lumbar puncture was done.

to these findings in dogs, for in man the analogous measurements from occiput to last lumbar spine approximate 575 mm.

Of equal importance to the change in cerebrospinal fluid pressure are the postural changes in the pressure of the cerebral venous system as determined in the sagittal sinus. In every experiment the magnitude of this change in cerebral venous pressure exceeded that of the

cerebrospinal fluid pressure: both changes were in the same direction. With no significant change in the intracranial arterial tension, it seems fair to conclude that the central nervous system is protected to a far greater extent against postural pressure-changes in the cerebrospinal fluid than against pressure-changes in the cerebral venous system.

Certain general speculations may perhaps with justice be made regarding postural changes in the pressure of the cerebrospinal fluid. That the hydrostatic column of the fluid does not exert its full effect upon the positive pressure of the cerebrospinal fluid which exists in the horizontal position, is due in part at least to the closed-box character of the bony coverings of the central nervous system. This view finds support in observations taken of occipital cerebrospinal fluid in which this pressure increased to a far greater extent on vertical tilting with head down after lumbar puncture than before (fig. 13); here the vertical, closed column is apparently vented and the atmospheric pressure may directly affect the column of cerebrospinal fluid in the spinal canal.

From all of these observations, it becomes quite clear that in the mammalian central nervous system there exist factors which modify extraordinarily the physical effects of the hydrostatic fluid column. According to the physics of the phenomenon, there would be no postural change in the cerebrospinal fluid pressure, if the spinal dura were actually held rigidly in place and if no change in the vascular bed could occur. If these two conditions held absolutely, there would be a completely filled fluid-column within a rigid system: on tilting to the vertical no displacement of fluid and no change in the normal positive pressure of the cerebrospinal fluid would occur. However, the fact that the pressure of this characteristic body-fluid does change when the animal is shifted from the horizontal to the vertical, forces one to assume certain biological phenomena. In the first place, it is apparent that the spinal dural tube serves in part as a rigid container as evidenced by the increased extent of the occipital cerebrospinal fluid pressure-change on tilting from the horizontal to the vertical after lumbar puncture. Secondly, the fact that there is a change of pressure in the cerebrospinal fluid on shifting from the horizontal to the vertical indicates either that the veins of the central nervous system are capable of sudden dilatation when the external pressure on them is lowered, or that a partial collapse of the spinal dura occurs, or that a combination of these two factors is operating.

It is possible to obtain some insight into the probable importance of these factors. If the dilatation of the veins of the central nervous system were the sole factor permitting these hydrostatic effects on the cerebrospinal fluid pressure, one would predict that tilting from the horizontal to the vertical tail-down position would give a greater pressure change than tilting from the horizontal to the head-down position, for the cerebral veins possess a far larger vascular volume than do the spinal. The opposite effect is customarily obtained, the average reduction in occipital cerebrospinal pressure on tilting to the tail-down position being 81.1 mm., in comparison to the increase of 103.3 mm. in tilting to the head-down position. In some animals, the reductions and increases obtained by these postural alterations are of exactly the same magnitude. The difference in these average pressure-changes thus forces one to believe that partial collapse of the spinal dura mater occurs in both postural alterations, for any explanation of the postural pressure-alterations based solely on venous dilatation is seemingly inadequate. It is likely therefore that when the animal be tilted to the vertical head-down position, partial collapse of the caudal portion of the dura occurs, probably with some dilatation of the adjacent spinal veins; these factors permit increase of the occipital cerebrospinal fluid pressure of slightly over 100 mm. In the opposite postural shift to the vertical tail-down position, partial collapse of the cervical (and upper thoracic (?)) dura mater must take place, accompanied probably by some dilatation of the veins in cerebral and cervical regions; the collapse of the spinal dura in this region however cannot be as great as in the reverse condition for the average reduction in occipital cerebrospinal fluid is but slightly in excess of 80 mm. In those animals in which the pressure-increases and reductions are of the exactly same magnitude, it is necessary to assume that the partial collapse of cervical and caudal portions of the dura mater are of the same extent physiologically. The importance of the factor of dilatation of the veins in the uppermost portions of the neural tube in the vertical position cannot be told; it may be a factor of but little significance.

Such explanations as just ventured cause one to inquire further into the correctness of the Monro-Kellie doctrine. It does not seem at all necessary to alter the view already expressed that "within tested physiological limits" the bony containers of the central nervous system serve as a closed box, for the experimentation on which this view

was based still remains sound. The production of negative pressures with the central nervous system indicates that the dura mater as a whole cannot collapse to the extent necessary to eliminate these pressures; the striking increase of occipital cerebrospinal fluid pressure on venting the fluid-column by lumbar puncture likewise indicates that the spinal dura does not entirely collapse in the vertical head-down position. It would seem therefore that regarding the "physiological limits" under which the Monro-Kellie thesis is correct, knowledge is increasing.

Under these circumstances, it seems logical to conclude that the central nervous system is not subject to the total hydrostatic effects of the entire column of cerebrospinal fluid in postural changes from the horizontal to the vertical positions. In the experimental four-footed mammal (cat and dog), the maximal observed effect is about one-third to one-fourth of the possible hydrostatic column; with these results the observations on human beings are in accord.

GENERAL CONCLUSIONS

To summarize briefly our knowledge of the cerebrospinal fluid is difficult at the present time, largely because of uncertainties which exist in our knowledge of critical phenomena regarding the fluid. But a few generalities may be made with profit; these generalities are not without speculative interest. In the first place, it seems fairly well established that the pressure of the cerebrospinal fluid is not identical with that of either the cerebral arteries or of the cerebral veins: it is, however, a relatively independent pressure, representing apparently the physiological balance between the processes of secretion and absorption of the fluid. This relatively independent pressure of the cerebrospinal fluid is however affected by alterations in the pressures of the cerebral arteries and veins. The pressure of the superior sagittal sinus (taking this pressure as indicative of the pressure in the cerebral veins) is almost invariably lower than the pressure in the cerebrospinal fluid. Variations in pressure in the cerebral veins effect changes in the pressure of the cerebral fluid; these changes in the fluid pressure are always in the same direction and of lesser magnitude. Changes in the pressure of the cerebrospinal fluid, likewise, effect changes in the pressure of the cerebral veins; these changes again are of lesser magnitude but in the same direction.

Recent observations have shown that the intravenous injection of

solutions of various concentrations can effect changes in the pressure of the cerebrospinal fluid, as well as in the cerebral arteries and veins. The strongly hypertonic solution causes marked decrease in the pressure of the cerebrospinal fluid; the isotonic solution, no lasting change; and the hypotonic solution, marked increase. Under these conditions, the pressure of the cerebrospinal fluid maintains its usual relationship to the pressure in the superior sagittal sinus, except after the injection of the strongly hypertonic solution when the conditions are reversed.

In any consideration of the factors maintaining pressure of the cerebrospinal fluid, regard must be had for the *Monro-Kellie* doctrine that at all times the contents of the cranium are practically invariable. This thesis, while modified to meet newer knowledge, is within certain physiological limits essentially correct, as demonstrated by experiments employing the negative pressures of the cerebrospinal fluid, brought about by the intravenous injection of strongly hypertonic solutions. No more important thesis in intracranial physiology exists than this, and that the doctrine should have survived a century and a half of persistent experimentation is in itself a phenomenon of great interest.

Posture plays an important rôle in the pressure of the cerebrospinal fluid. The tilting of four-footed laboratory mammals from horizontal to vertical positions causes marked changes in the pressure of the cerebrospinal fluid, but these alterations in the pressure of the fluid are far less in extent than would be expected if consideration is given only to the hydrostatic height of the fluid-column above the recording needle. Here again, the *Monro-Kellie* doctrine assumes importance for it is obvious that the bony coverings of the central nervous system constitute within limits a physiologically closed system, so that the full height of the hydrostatic column is not thrown upon the dependent part of the central nervous system.

DISCUSSION

The following questions submitted to Dr. Weed before the Commission together with the answers to them, are here reported verbatim.

DR. JAMES B. AYER: I should like to ask Dr. Weed if he did a craniectomy and then carried out this procedure.

DR. WEED: I should like to answer Dr. Ayer by saying I have not carried out this procedure, largely because of technical difficulties. With this experimental

set-up, you would still have to leave the dura intact in order to make any measurements of pressure. You would then have the problem of dealing with the dura exposed to atmospheric pressure, and we know that the collapse of the dura under those conditions is very slight unless your cranial defect is very large.

DR. AYER: I think you just said your head-up and head-down position is maintained for about ten minutes. I think on the chart your venous pressure, which was considerably greater in variation, tended subsequently towards the end of that period to approach the pressure level of the cerebrospinal fluid. Is that correct?

DR. WEED: Yes, the cerebral venous pressure exceeded the pressure of the cerebrospinal fluid in many cases, when the animal was in the vertical head-down position. In one particular animal, starting out with an intracranial venous pressure of 85 mm. and a cerebrospinal fluid pressure of 125, by tilting the animal we obtained a pressure in the cerebrospinal fluid of 230 mm. and 410 in the intracranial venous pressure, showing the protection of the central nervous system against possible changes in the venous pressure was much less than against the changes in the cerebrospinal fluid pressure (*i.e.*, intracranial tension itself); subsequently the two pressures became of somewhat the same magnitude.

DR. AYER: Subsequently as time went on they equalized?

DR. WEED: They might or might not. There is no general law.

DR. LEWELLYS F. BARKER: In the acute process I would like to ask whether the conditions of the experiments were compatible with the study of prolonged change in posture, and whether any biological effects became noticeable.

DR. WEED: I rather doubt if we could use the method at all for a study of prolonged reactions because vasomotor collapse occurs very frequently in these animals particularly in those animals in which abrupt tilting from horizontal to vertical positions has been carried out five or six times. We find that the vasomotor mechanisms of these animals go all to pieces. Of course they are four-footed laboratory mammals which are accustomed to a horizontal rather than a perpendicular life. I should like to carry out experiments to find out if there are any biological readjustments.

DR. CONRAD BERENS: Has Dr. Weed any experimental evidence to show that increased intracranial pressure in man results in increased pressure in the cerebral arteries? If increased pressure in the arteries has been noted, is the diastolic pressure increased more than the systolic pressure?

This question is asked because the diastolic pressure in the retinal arteries seems to be more affected than the systolic pressure.

DR. WEED: I have no information on this question at all. I think the only evidence we have that increased arterial pressure has an influence on cerebrospinal fluid pressure is that both animals and man have higher pressure in advancing age. It is a biological fact.

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CHAPTER IV
INTRACRANIAL PRESSURE CHANGES DURING FORCED
DRAINAGE OF THE CENTRAL NERVOUS SYSTEM:
THE HYDRATION FACTOR¹

LAWRENCE S. KUBIE, M.D.

BY "FORCED DRAINAGE" is meant the administration of water by mouth, or the intravenous or subcutaneous injection of hypotonic saline solution, at the same time allowing the free escape of the cerebrospinal fluid. A series of recent studies led to the conclusion that by this procedure it is possible to accelerate markedly the formation of cerebrospinal fluid (3). Furthermore, it was observed that the application of this process of "forced drainage" to an animal suffering from encephalomyelitis caused a remarkable extrusion of the perivascular cellular exudates from the depths of the tissue into the subarachnoid space. Such a phenomenon is illustrated in figures 14 and 15, which are taken from the spinal cord of a cat which had been subjected to a prolonged trypan blue meningitis, with forced drainage instituted just before death. On one side a plug of lymphocytes is seen in the perivascular tissue in the depths of the cord, while at another point the lymphocytes lie in a heap over the opening of the perivascular channel into the subarachnoid space. In the higher magnification of figure 16, a zone of phagocytes filled with trypan blue can be seen along the outer border of the mound of lymphocytes (taken from the study of Kubie and Shults (3)).

The possibility of instituting in this way a physiological lavage of the central nervous system, with a partial washing out of inflammatory processes from the depths of the tissues to their surfaces, arouses a hope of therapeutic application. It is with serious misgivings, however, that one faces the possibility that the procedure of forced drainage might result in a dangerous increase of intracranial pressure. The aim of this communication is to demonstrate that during forced drainage an entirely negligible rise in intracranial pressure occurs,

¹ From the Laboratories of the Rockefeller Institute for Medical Research.

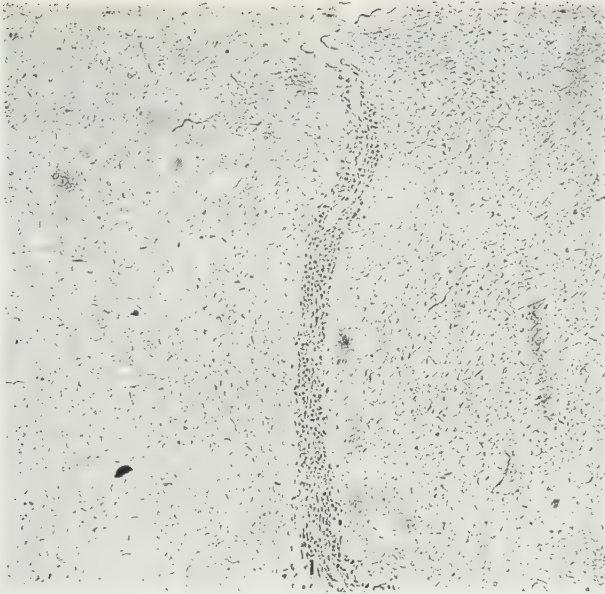


FIG. 14. KC 12 X. Lymphocytic infiltration in the perivascular tissues of a cat suffering from a trypan blue meningo-encephalitis. A short forced drainage, instituted just before death, had been prematurely terminated by an overdose of anesthetic. $\times 200$.

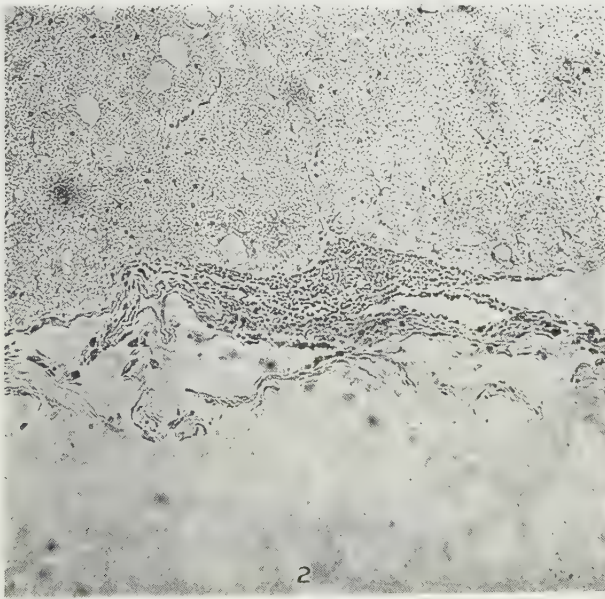


FIG. 15. KC 12 X. Lymphocytic infiltration extruded from the perivascular channel of the same animal as in figure 14, and lying in the subarachnoid space. $\times 200$.

and no demonstrable hydration of the tissues of the central nervous system. The results of previous studies of the question will be presented briefly; and the investigations which have just been completed will be described in greater detail.

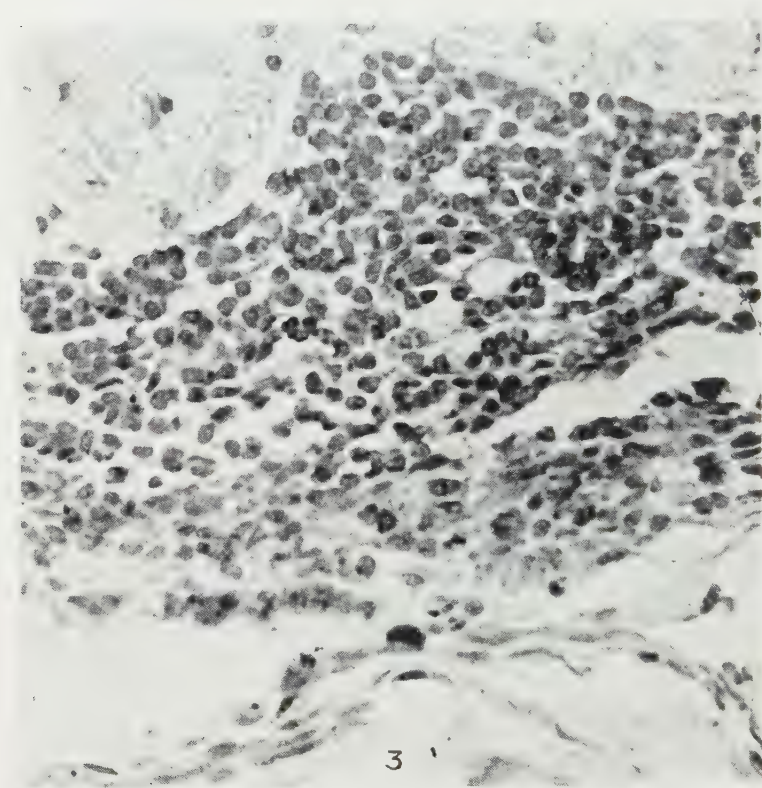


FIG. 16. KC 12 X. Same as figure 15, at 700 magnification. The contrast between the macrophages of the outer zone, filled with ingested trypan blue, and the deeper zone of lymphocytes is just visible in the photograph.

The problem was first studied on a group of normal, anesthetized dogs (1). Figure 17 (from the report of this study) shows the method used for measuring intracranial pressure while allowing a free flow of cerebrospinal fluid from a needle in the cisterna magna. As a result of this investigation, it was possible to conclude that during forced

drainage the intracranial pressure (which had dropped nearly to zero during the preliminary drainage) never rose above, and only rarely reached the initial normal level.

The second investigation of the question was undertaken during this past summer, in the Massachusetts General Hospital and the Children's and Infants' Hospitals of Boston, through the kindness of

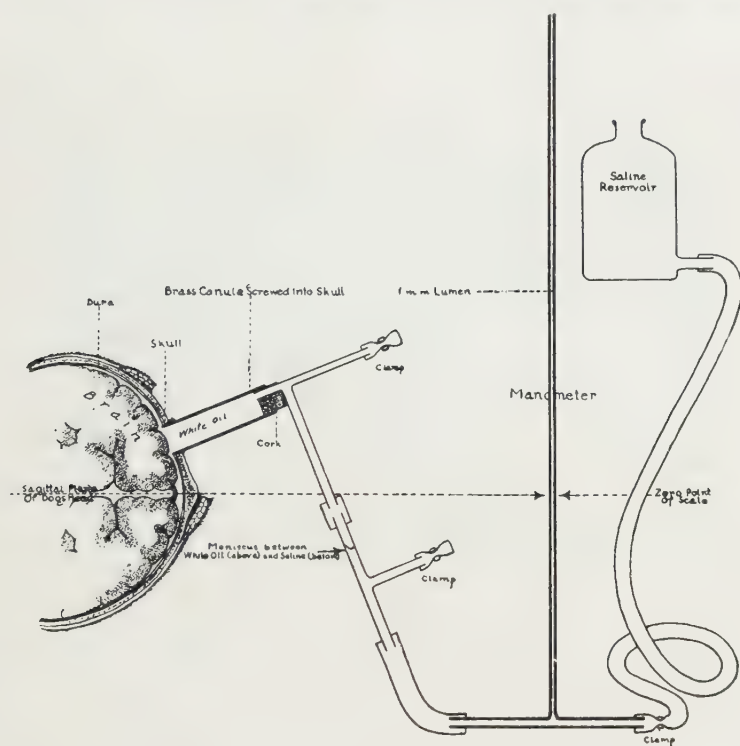


FIG. 17. Method of measuring intracranial pressure with free drainage of the cerebrospinal fluid (see text from Kubie (1)).

Dr. James B. Ayer, Dr. Bronson Crothers, and Dr. Kenneth Blackfan. The full report of this work will appear in an early number of the *Archives of Neurology and Psychiatry* (2). Examinations were made of patients who were suffering from many forms of infection of the central nervous system; and on them, obviously, no direct measurements of intracranial pressure could be made if the cerebrospinal fluid

was to be allowed to escape freely from a needle in the lumbar subarachnoid space. It was argued, however, that if a significant increase in intracranial pressure occurred under these conditions, it would be due to a tapping of fluid in the ventricles and a diffuse hydration of tissue. The result of this would be that the swollen nervous system would respond as does one in which the continuity of the cerebrospinal fluid spaces was interrupted by the presence of a tumor. In short, if the intravenous administration of hypotonic salt solution caused a significant amount of swelling of the brain, despite the fact that the cerebrospinal fluid was allowed to escape during the injection, then jugular compression would give the characteristic reaction of "spinal block," with little or no output of fluid and little or no rise in pressure in a manometer attached to the lumbar needle. In no case was it possible to see any evidence of the existence of such a condition of "block," the pressure or outflow responses being quite as prompt and quite as extensive as before the injection.

This observation, while reassuring, was not perhaps conclusive. It is possible, however, to present at this meeting direct histological evidence of the absence of any hydration of the nervous system during forced drainage.

EXPERIMENTAL DATA

The observations have been made on normal animals under sodium veronal anesthesia: eight rabbits and four dogs. The animals were taken in pairs of approximately equal weight, and to each pair equivalent or identical injections of hypotonic saline were given at the same rate. One and one-half hours before the experiment each animal was anesthetized by giving 0.3 gram Na veronal intravenously, thereby producing a satisfactory and steady narcosis. In a few cases, a whiff of ether was given at the onset of the experiment—and if this was done to one animal, it was also given to the other of the pair. Thus, each pair of animals was subjected to identical treatment, except that one animal was given the injection without allowing the cerebrospinal fluid to escape, while from the cisterna magna of the other animal the cerebrospinal fluid was allowed to flow freely, both before and during the administration of the hypotonic salt solution.

Immediately after the injection, the brains and cords were exposed widely in their bony framework, as far as possible avoiding injury to the dura. The bony skeleton, trimmed down to a minimum, was

freed from the rest of the body and then immersed in 10 per cent formalin. The formalin was made up in saline of the same strength as that which had been injected during the experiment. In some experiments symmetrical blocks were also cut in a few minutes and placed in Zenker's fluid. Intravascular injections of fixative were not given for fear that the pressures used might introduce post-mortem deformation; and perfect cytological fixation was willingly sacrificed for the sake of the preservation of the relation of parts. The sharpness of the contrasts obtained seems to justify the method of fixation chosen.

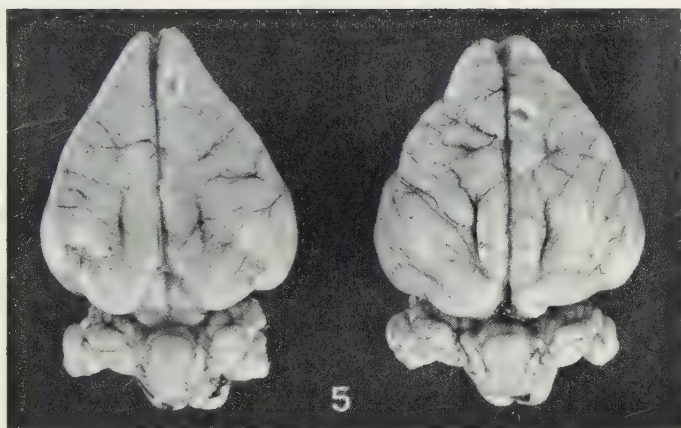


FIG. 18. K 96 A (marked "96" in the photograph) and K 97 A, described in protocols and in text. Contrast between the swollen brain of the undrained and the normal appearance of the drained animal.

RESULTS

The contrast between the animals which had been drained and those which had not been drained could be clearly made out both on gross inspection and under the microscope.

In figure 18 the dorsal surfaces of the forebrains of two rabbits are shown. The brain of the undrained animal is immediately recognizable by the swollen, rounded, forward poles, the full sides, and the occipital poles which bulge so markedly as to hide completely the underlying corpora quadrigemina.

In figure 19 is reproduced an exact camera lucida (Edinger appara-

tus) tracing from another pair of rabbits. Here the spinal cord of the undrained animal is so swollen as to fill almost completely the dural cuff; the fissures and furrows are nearly obliterated, the central canal is ballooned out, and fluid-filled spaces are seen in the dorsal and ventral median fissures, while the mouths of the fissures are occluded at the surface. In contrast to this, the cord of the animal

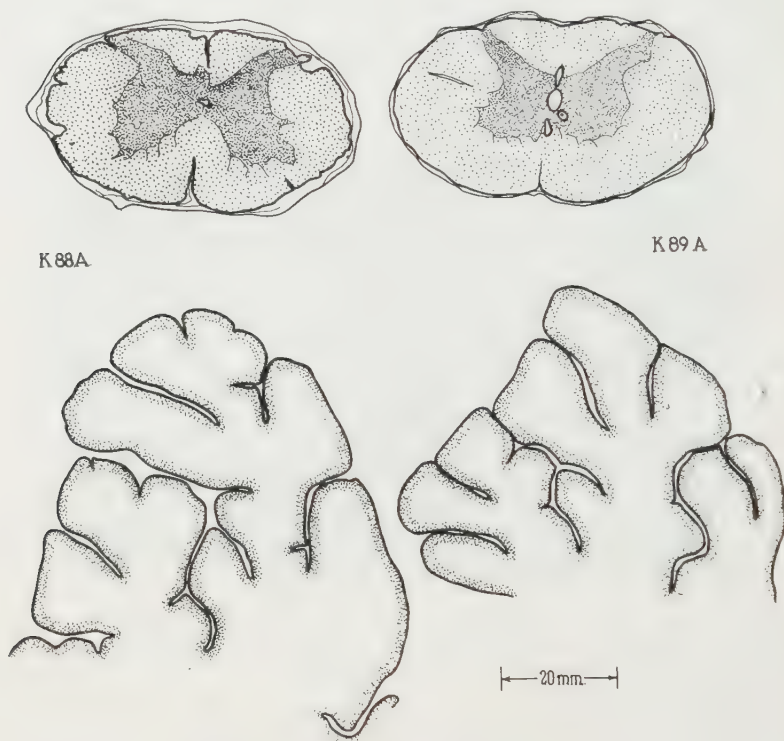


FIG. 19. Contrast between the deep hydration of tissues in the undrained animal and the lack of hydration in the drained animal (see text and protocols).

which was drained throughout the injection lies loosely in the dural cuff, the periphery is dented by deep fissures, the central canal is small and folded, and no deep collections of fluid can be seen.

Similarly, the cerebellar sections show distinct differences. That from the undrained animal is flattened at the surface, with occlusion of the mouths of the sulci, and fluid trapped in the depths; whereas the other has rounded folia and widely open sulci.

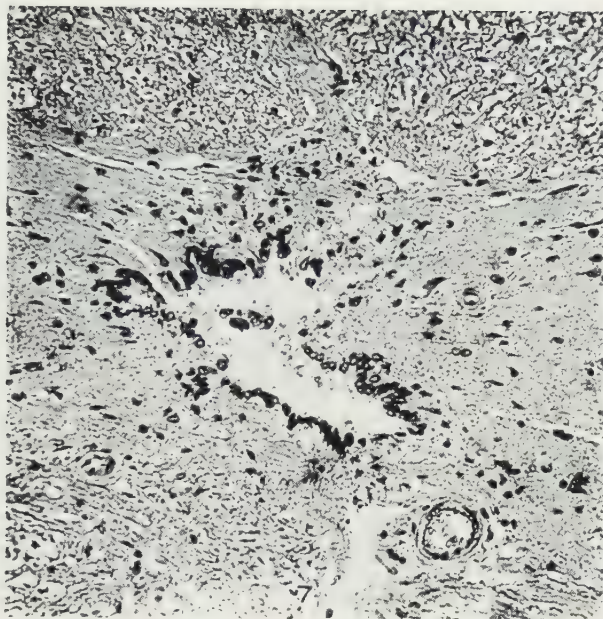


FIG. 20. Undilated central canal from drained animal, K 88 A. $\times 300$



FIG. 21. Tremendously dilated central canal from undrained animal, K 89 A $\times 300$.

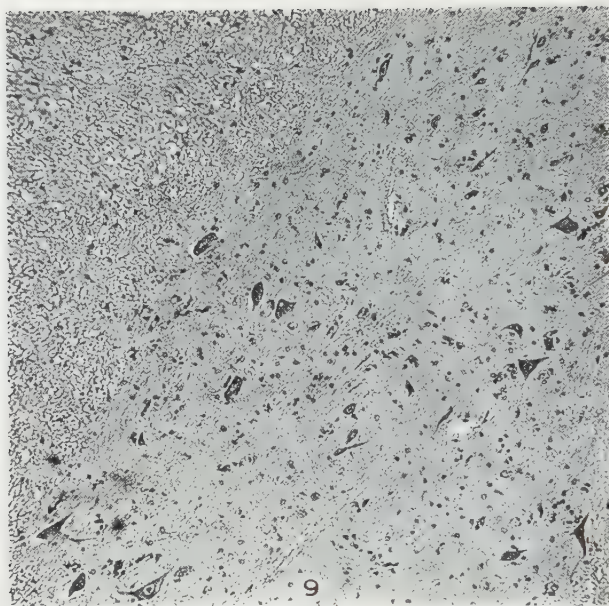


FIG. 22 Undistended perineuronal spaces from drained animal, K 88 A. $\times 140$.

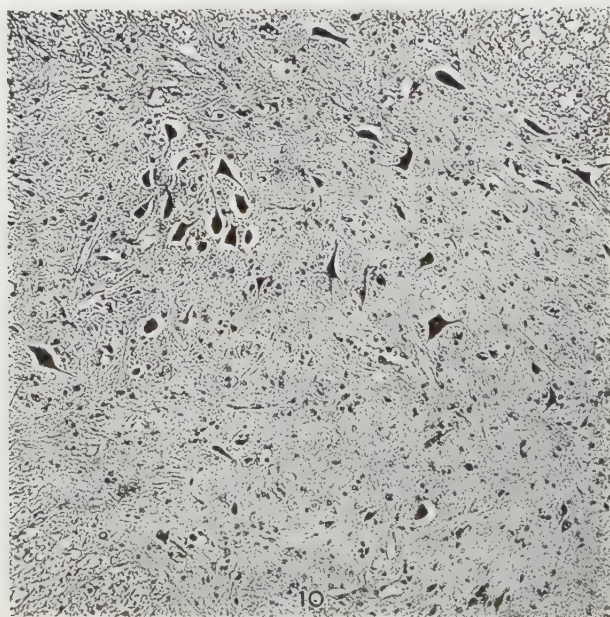


FIG. 23. Tremendously distended perineuronal spaces from undrained animal, K 89 A. $\times 140$.

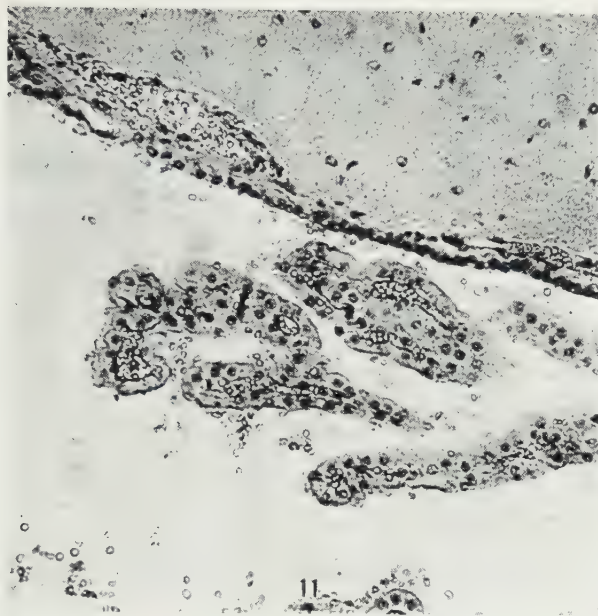


FIG. 24. Unvacuolated chorioid plexus from the drained animal, K 88 A.
 X300.

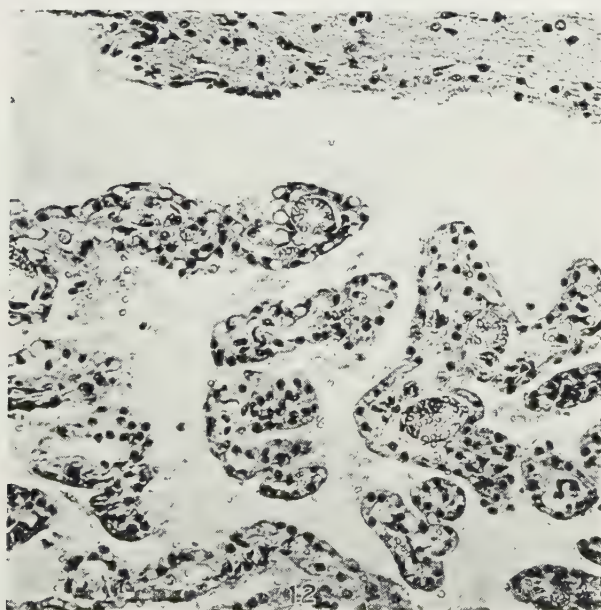


FIG. 25. Vacuolated chorioid plexus from the undrained animal, K 91 A.
 X300.

In figures 20 and 21 the contrast between the central canals is shown at greater magnification, demonstrating the tremendous distention of the one, while there is complete absence of any such deformation of the central canal from the cord of the drained animal.

In figures 22 and 23 the great dilatation of the perineuronal spaces in the grey matter of the spinal cord is seen in the rabbit which was

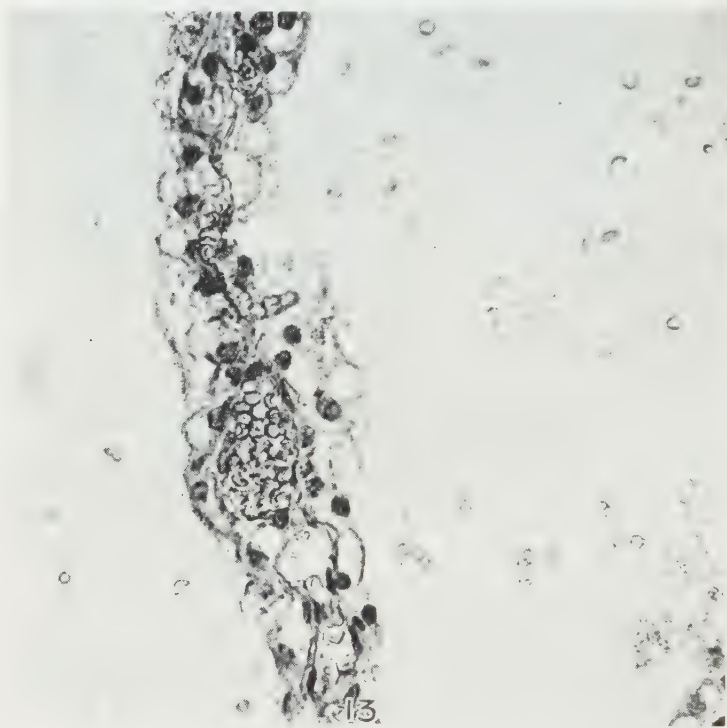


FIG. 26. Vacuolated choroid plexus from the undrained animal, K 89 A. $\times 510$.

not drained, in contrast to the lack of any such dilatation of these spaces in the other.

The pictures presented here, of the hydration of the tissues of the central nervous system as a result of the intravenous injection of hypotonic solutions with the cranio-vertebral cavity intact, confirm in every detail the findings of Weed (4). Similarly, these observations

TABLE II
PROTOCOLS

	WEIGHT	NaCl SOLU- TION	AMOUNT	DURA- TION	VENOUS PRESSURE		CEREBROSPINAL FLUID
					Before injection	After injection	
					mm. saline		
	grams	per cent	cc.	minutes			
<i>Rabbits:</i>							
K88A.....	2000	0.45	250	40	80	75	Drained
K89A.....	1975	0.45	250	42	100	95	Not drained
K91A.....	2000	0.45	475	30	75	105	Not drained
K92A.....	1950	0.45	450	30	70	110	Drained
K93A.....	1900	0.45	250	20	80	90	Not drained
K94A.....	1900	0.45	250	20	85	80	Drained
K96A.....	1700	0.35	250	25	80	78	Drained
K97A.....	1750	0.35	250	25	95	85	Not drained
<i>Dogs:</i>							
K94.....	13300	0.40	750	55			Drained
K95.....	10200	0.40	650	50			Not drained
K98A.....	4520	0.40	450	65	125	120	Drained
K99A.....	6800	0.40	650	60	110	125	Not drained

The injections were made from a calibrated Woulfe bottle which was kept at body temperature in a water bath. A constant, measured head of pressure was maintained in a large pressure reservoir. The venous pressures were determined before and after the injection by connecting a small-bore stand-pipe manometer with the side arm of a T-tube which was inserted in the rubber tubing which led from the Woulfe bottle to the animal. The manometer was filled with the injection fluid, the tubing from the Woulfe bottle pinched off, and the level at which the fluid from the manometer ceased to run into the animal's vein gave a direct determination of venous pressure.

It is important to note that such large volumes of hypotonic solution can be injected slowly without materially altering venous pressure. This indicates that when the injections are made slowly the excess fluid must leave the circulation almost as rapidly as the fluid is injected, so that little increase of blood volume results and no great strain is placed upon the heart.

concur with his statement (*loc. cit.* p. 271) that, "It is doubtful whether the nerve cells themselves participated in the process."

Furthermore, when Weed and McKibben ((5), pp. 541 and 545) compared these effects with those produced by similar injections which were given after making extensive openings in the skull and in the dura, they could find no evidence of such hydration in the animals with open heads. The present studies have shown that it is not necessary to make any such wide decompressions in order to prevent hydration of the nervous system, but that under the experimental conditions it can be equally well achieved merely by a continuous drainage of cerebrospinal fluid. That there must be some limit beyond which the brain will swell faster than the fluid can escape would seem to be inevitable: but the studies so far completed have not established where this limit lies.

Finally, in figures 24, 25, and 26, it is seen that the same marked contrast exists in the picture of the chorioid plexus. The plexus from the drained animal shows no vacuolation; that of the undrained animal is swollen with huge, water-filled vacuoles. The significance of this surprising observation is not entirely clear, and is being subjected to further study. It suggests either that the vacuolation is not a sign of the passage of water through the plexus but rather of increasing intraventricular pressure, or else that when the cerebrospinal fluid is allowed to drain during the injection the passage of water from the blood stream into the cerebrospinal spaces takes place not through the plexus, but more diffusely.

CONCLUSIONS

1. Under narcosis, large volumes of hypotonic solutions can be injected into animals without materially raising venous pressure, if the injections are made slowly.

2. *If no escape of cerebrospinal fluid is allowed*, such injections result in a marked rise in intracranial pressure, with a striking hydration of the central nervous system.

3. In the gross, this hydration is manifested by diffuse swelling of the brain. In sections, the fluid is found predominantly in certain well-defined loci: *i.e.*, the ventricles and central canal, the chorioid plexus, the perineuronal spaces, and the perivascular channels. No recognizable hydration of the neurones themselves occurs, and relatively little diffuse interstitial edema.

4. If free escape of cerebrospinal fluid is allowed, the same injections produce little rise in intracranial pressure, and no recognizable hydration of the tissues of the central nervous system: *i.e.*, the ventricles and central canals remain undistended, the chorioid plexus free of vacuoles, the perineuronal spaces and perivascular channels not dilated.

5. It is evident, therefore, that lowering the osmotic pressure of the blood by the intravenous administration of hypotonic solutions causes a transudation of fluid from the capillaries into perivascular and perineuronal areas throughout the whole central nervous system; and that by simultaneously draining the cerebrospinal fluid a free escape of this transudate is made possible from the depths of the tissue to the surface through some pathway of least resistance (presumably the perivascular channels).

6. This procedure can cause a washing-out of perivascular exudates into the subarachnoid space, in experimental meningo-encephalitis in cats.

7. It is suggested that these observations demonstrate that forced drainage is a safe and rational procedure to attempt in the treatment of many kinds of infection of the central nervous system in man.

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CHAPTER V

THE EFFECT ON HUMAN CEREBROSPINAL FLUID PRESSURE OF EXTRACTION AND INJECTION OF FLUID

WITH OBSERVATIONS ON THE TIME OF NORMAL READJUSTMENT

H. C. SOLOMON, M.D.

THIS presentation summarizes studies on the reaction of the cerebrospinal fluid pressure after a disturbance of the normal level. Experience has taught that there is a considerable difference of pressure in different individuals. In conditions of average health or in disease conditions where there is no definite evidence of an increased intracranial pressure, the cerebrospinal fluid pressure as measured with a manometer connected with the lumbar puncture needle when the patient is lying on his side varies from 100 mm. of fluid to 250 mm. However, punctures made at intervals on the same patient show that the pressure tends to have a constant level. In other words, there is evidence of a mechanism which keeps the fluid pressure in a state of equilibrium. No attempt will be made at this time to discuss the factors which take place in this equilibrating mechanism. It may be mentioned, however, that the amount of blood in the head, the secretion and absorption of cerebrospinal fluid, and the elasticity of the spinal sac are all factors that play a part.

The first group of experiments deal with the withdrawal of cerebrospinal fluid by means of a lumbar puncture and the observation of the spinal fluid pressure for a period subsequent to this. The first three figures (figs. 27-29) show that when all the fluid that will run out from the needle has drained off, producing a zero pressure in the manometer, in a period of a few minutes a rise in pressure occurs and the rise continues for a considerable period of time. The rate of increase varies considerably in different patients and occasionally it will be found that the return of pressure is quite rapid, so that at the end of forty to sixty minutes the pressure may have returned to two-thirds or three-fourths of its original level. In other cases the return is very much slower indeed. After the pressure has risen, it is found that fluid will flow again from the puncture needle and after all that

will come freely is withdrawn, the pressure will be found to be zero. These observations are made with the lumbar puncture needle remaining *in situ* preventing a leakage of fluid in the opening made in the meninges. (If the needle is withdrawn and the puncture again performed at the end of an hour, more or less, thereafter it will often

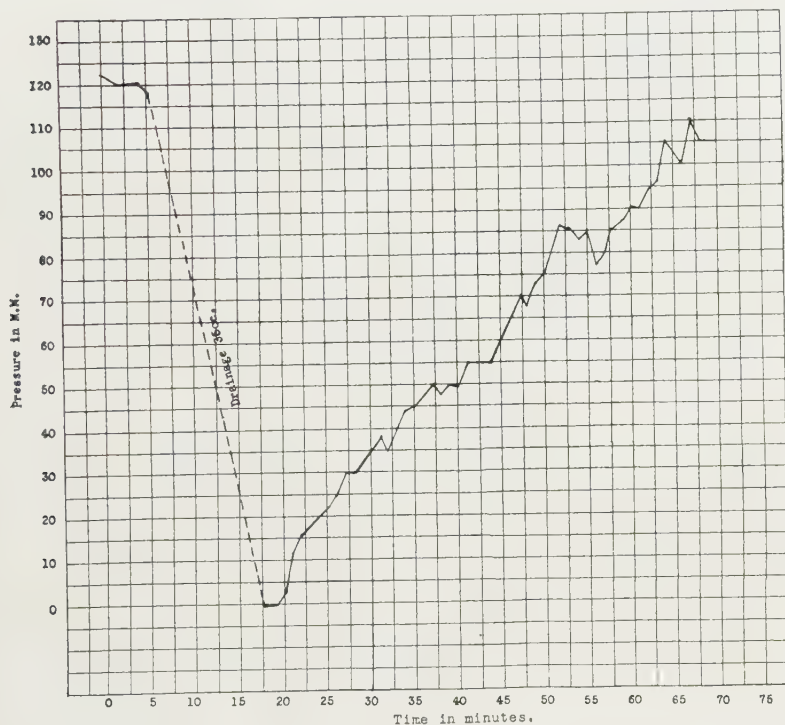


FIG. 27. A rapid increase in pressure occurred following drainage. This patient has been under treatment for a number of years and is able to get off the table after drainage and carry on his customary activities with no ill effects.

be found that the pressure is very low and many times as late as twenty-four hours after the first puncture no fluid will run out of the needle unless aspirated. This is probably due to leakage through a hole in the dura, which means that the situation is entirely artificial and is not to be confused with the equilibrating effect above-mentioned.)

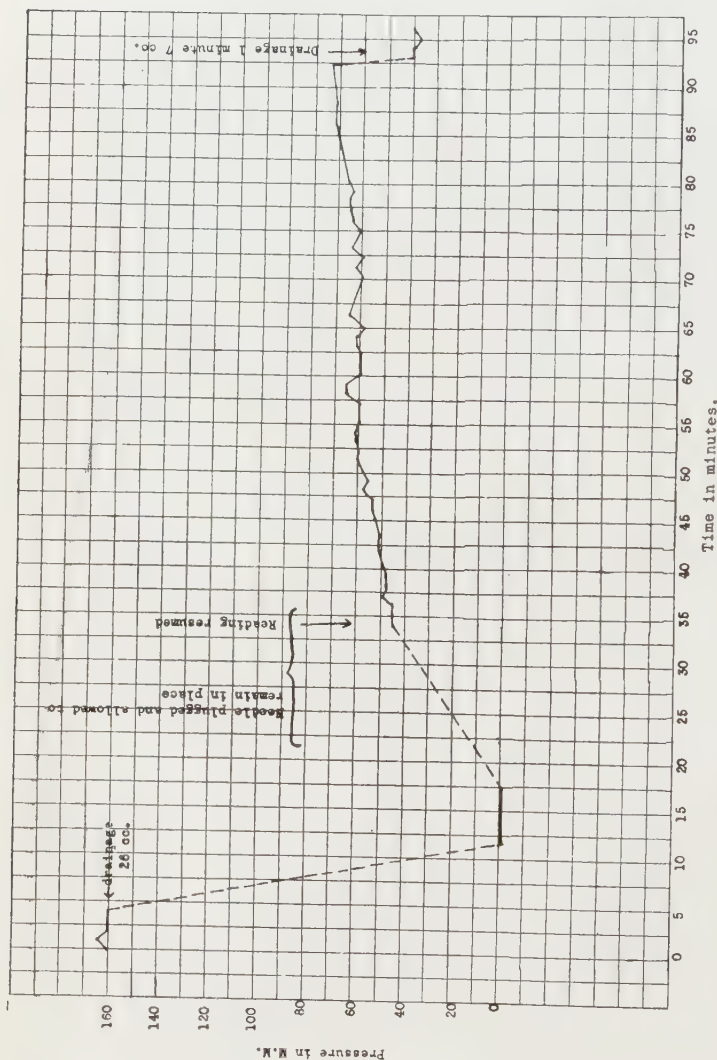


FIG. 28. During the first six minutes of drainage 24 cc. of fluid flowed out. Then 2 cc. more were removed in a syringe. Following this no fluid fell from the needle in thirty seconds, although a drop could be seen. When the manometer was attached the pressure registered essentially 0 for five minutes—there was possibly a slight increase in pressure.

The stylet was then replaced in the needle, which was left in place fifteen minutes. The manometer was then attached and a pressure of 45 mm. recorded. Readings were taken every minute for over an hour and in that period the pressure rose to 73 mm.

When the fluid was allowed to drain, it dropped rapidly from the needle so that in one minute 7 cc. were collected. This caused a fall in the pressure to 40 mm.

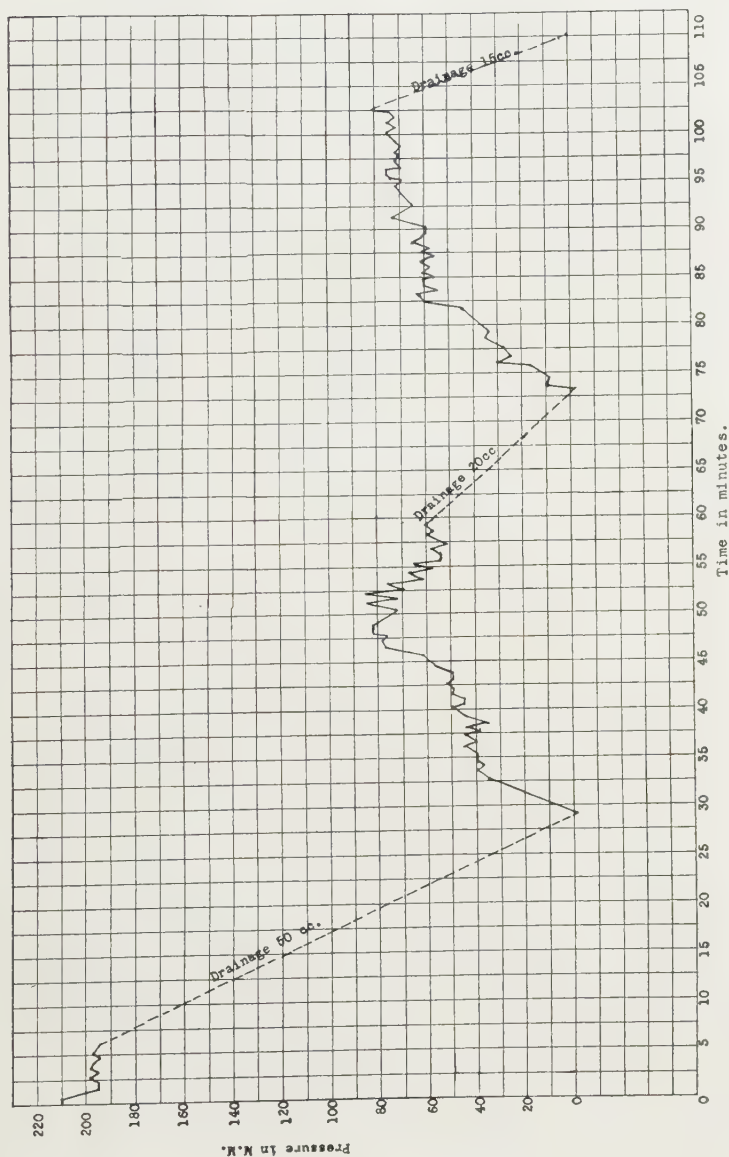


FIG. 29. Patient was quiet and cooperative most of the time but occasionally raised his head for a few seconds—this almost invariably caused a rise in the pressure.

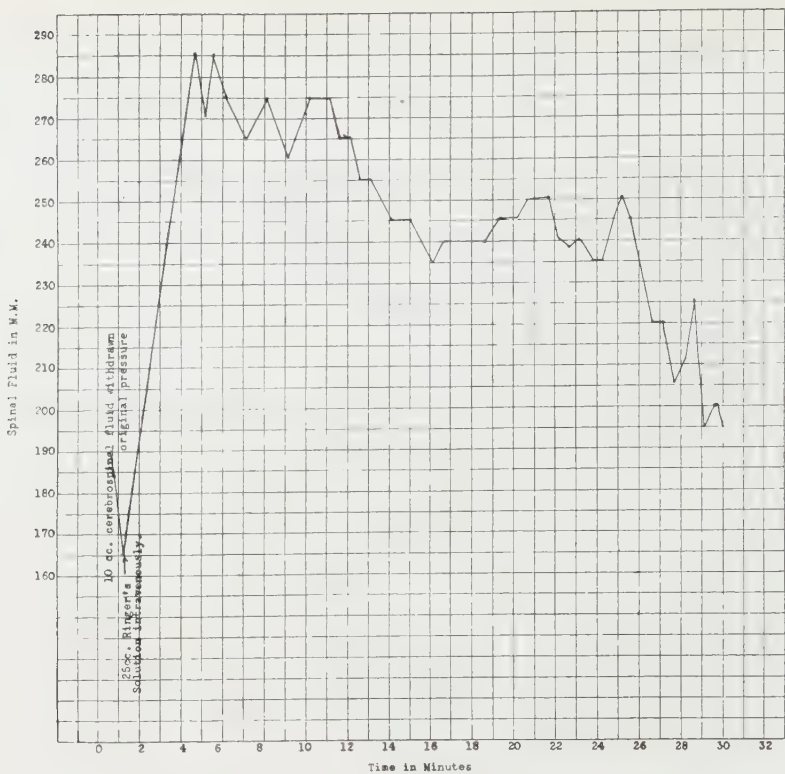


FIG. 30. Production of hypertension and return to normal

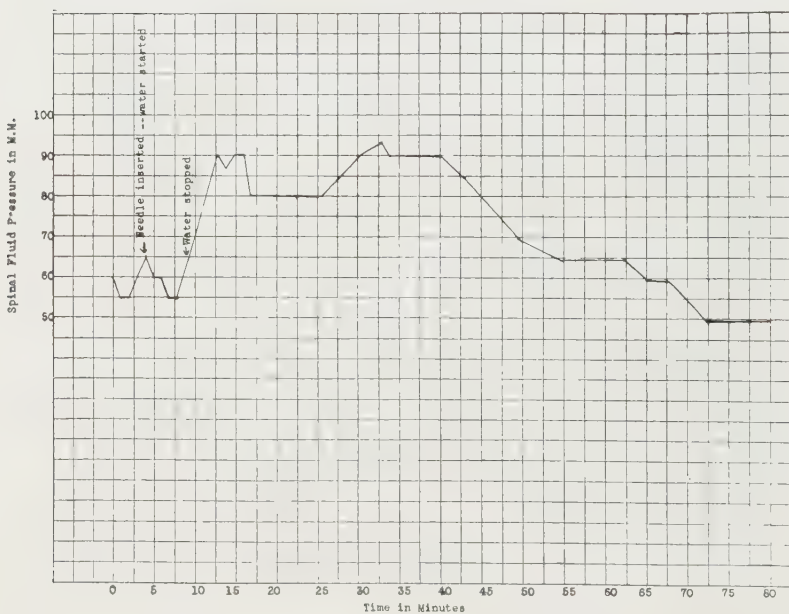


FIG. 31. Effect on spinal fluid pressure of the intravenous injection of 200 cc of distilled water.

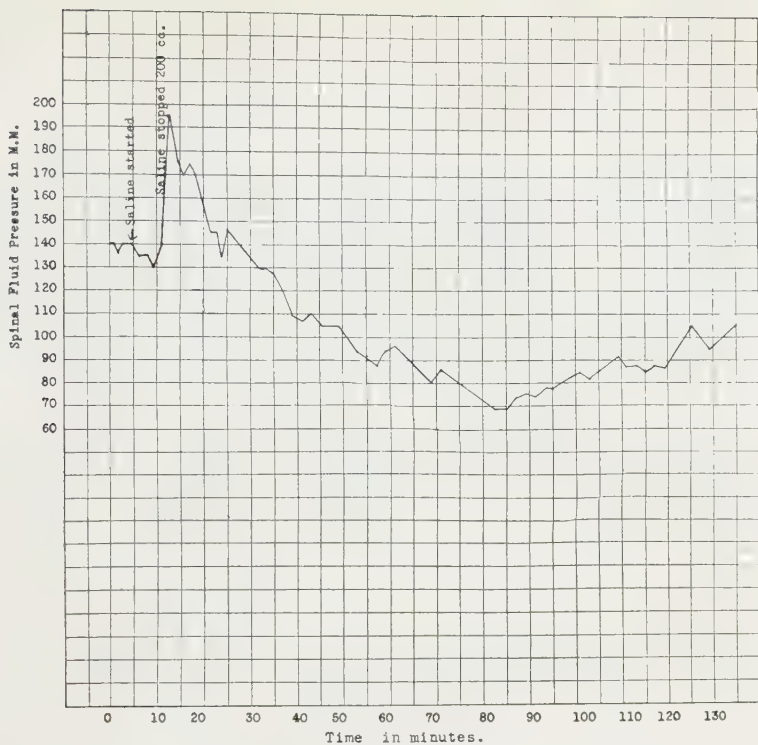


FIG. 32. Effect on spinal fluid pressure of the intravenous injection of 200 cc. of distilled water.

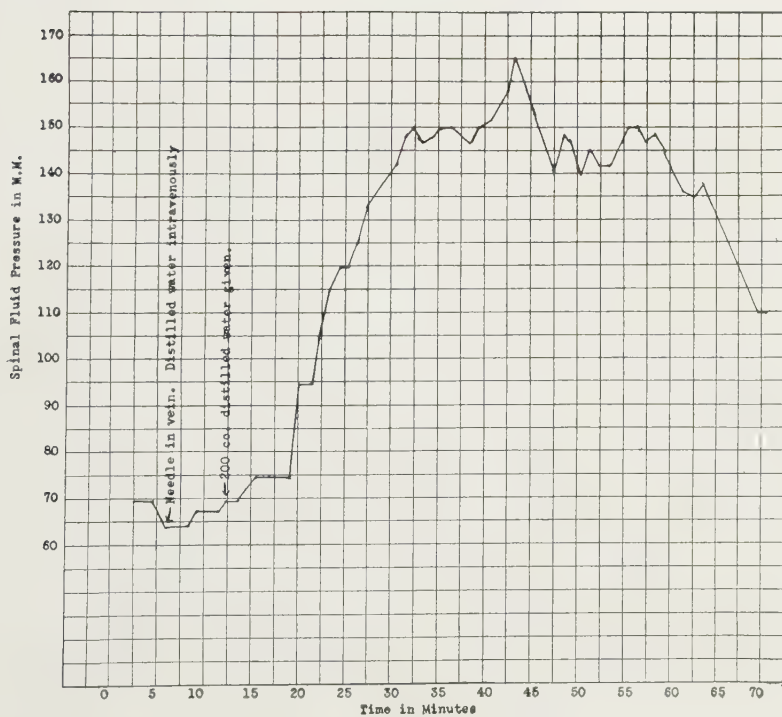


FIG. 33. Effect on spinal fluid pressure of the intravenous injection of 200 cc. of 15 per cent NaCl.

The fourth figure (fig. 30) shows the effect of introducing Ringer's solution, and thereby increasing the amount of fluid in the subarachnoid space. This at once increases the pressure, but in the course of a few minutes the pressure regains its original level. Headache is often complained of by the patient when the fluid has been introduced and the pressure raised. This headache is of quite brief duration

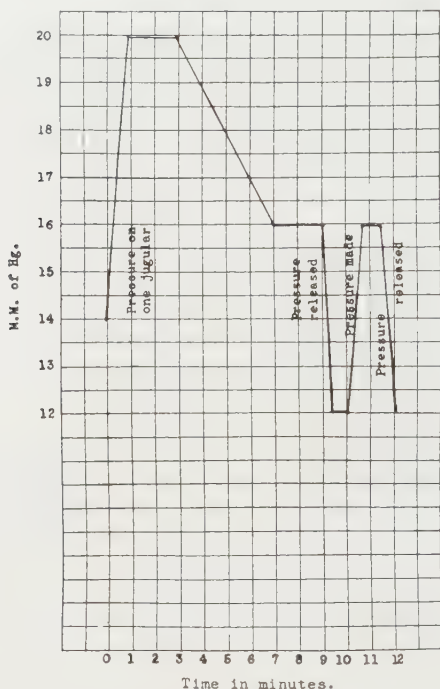


FIG. 34. Spinal fluid pressure on one jugular vein

and within a few minutes of the drop in manometric pressure the headache disappears.

Figures 31, 32, and 33 show that after the cerebrospinal fluid pressure has been decreased by the intravenous injection of hypertonic salt solution, or increased by the intravenous injection of distilled water, after a period of approximately an hour the pressure begins to return in the direction of its original level.

The last figure (fig. 34) shows that if the pressure is increased by

shutting off the return of fluid from one jugular vein, in the course of two or three minutes the pressure again tends to fall to its original level.

These observations demonstrate the ability of the organism to correct changes in the cerebrospinal fluid pressure produced by various means. In the cases where the large amounts of fluid are withdrawn, it would seem that the formation of new fluid must play a part in the return of the normal pressure, as it does not seem probable that an increased amount of blood within the vessels of the brain, to the extent of 60 or 70 cc., takes place. We have further confirmation of the ability of the secreting mechanism to supply large amounts of fluid in the cases of injury, allowing the outflow of fluid from the subarachnoid space to the amount of more than 1000 cc. in twenty-four hours. The ability of the mechanism to compensate for the increased pressure allows one to form the hypothesis that, in cases of new growths within the cranium, the organism should be able to maintain a relatively normal pressure for a time until the growth becomes of size beyond which this mechanism is no longer capable of compensating. It is probable, therefore, in the case of tumors so located that they do not greatly impede the normal flow of cerebrospinal fluid, that they may obtain considerable size before evidence of increased intracranial pressure becomes evident.

DISCUSSION

The following questions submitted to Dr. Solomon before the Commission, together with the answers to them, are here reported verbatim.

DR. WILLIAM G. SPILLER: I should like to ask whether there is any difference according to the age of a person in whom this test is made as to the rapid or slow flow of the spinal fluid.

DR. H. C. SOLOMON: I regret very much that I have not analyzed that, so I do not know. I will look it up and see if I can find any relationships or any differences.

DR. AYER: Were these tests made on normal individuals?

DR. SOLOMON: Some were perfectly normal individuals. There is no difference observed in regard to that.

DR. AYER: I suspect that you might have something to say about disease processes. Have you?

DR. SOLOMON: I have nothing to say about the situation in disease processes. The luetic group have a higher pressure on the whole. We have some observations with pressures of 80 or 90 mm. fluid and some with 250, and in the various psychiatric conditions the same thing is true; there is some variation, but on the whole they tend to fall in the same group between average normal 100 and 200 mm. pressure.

DR. WALTER FREEMAN: What is the course of the pressure of the cerebrospinal fluid in the twenty-four hour period following spinal drainage? Is there oversecretion of fluid thus provoking hypertension and headache?

DR. SOLOMON: That brings out one of the problems that is very difficult to handle on a human patient because of the necessity of making frequent punctures, but I have a good many observations on hand now which show there is a very great difference. In some individuals there will be a complete drop of fluid pressure at the end of twenty-four hours so that no fluid can be obtained except by suction. In others, there will be an increase in pressure over what it was the preceding day. This latter group is quite small, but we occasionally find them, and then some of these patients have lumbar puncture headaches, so-called, and a second puncture relieves them of their headaches. Those with the zero pressure, or negative pressure, are made no better certainly by lumbar puncture. These charts that I showed are made, of course, with the lumbar puncture needle in situ. If one removes the lumbar puncture needle before an hour and then does a second lumbar puncture, a very great drop in pressure may be found. In a few cases we did a puncture, simply measured the pressure, withdrew the needle and at the end of an hour did another lumbar puncture and the fluid pressure was much reduced, apparently indicating that there had been some leakage.

DR. MACROBERT: Is there not always a negative spinal fluid pressure during lumbar puncture headache?

DR. SOLOMON: We have had some experience, not a great deal, where there was an increased pressure when the second lumbar puncture was made at the end of twenty-four hours, with relief following a drainage of fluid. These are rare but they do occur.†

CHAPTER VI

THE CEREBRAL CIRCULATION

OBSERVATIONS OF THE PIAL CIRCULATION DURING CHANGES IN INTRACRANIAL PRESSURE¹

H. G. WOLFF, M.D., AND H. S. FORBES, M.D.

INVESTIGATION of the cerebral circulation during periods of increased intracranial pressure was given renewed impetus by Cushing (1), (2), (3). He demonstrated the existence of a hind-brain regulatory mechanism and showed that partial anemia of the vasomotor center might bring about a rise in systemic blood pressure great enough to maintain cerebral circulation during excessive elevations of intracranial pressure. In addition to his manometric studies Cushing observed the pial vessels through a window placed in a trephine hole in the skull in dogs. During the period of increased pressure within the skull he noted collapse of the sagittal sinus, distension and stasis in the tributary veins, and obliteration of the arteries and arterioles, with blanching of the cortex.

Making use of a recently developed technique we have reinvestigated the effect on the pial blood vessels of large rises in intracranial pressure. Our object has been to learn by actual measurement and observation with a microscope how the blood supply of the brain is affected by measured changes of pressure within the skull.

Our observations confirm those of Cushing and add further details of a quantitative nature.

METHOD

The method employed has been described in detail (4). In brief, measurements, observations and photographs of pial blood vessels have been made, by microscope, through a cranial window in anesthetized cats. Record of blood pressure in the femoral artery has been made at the same time.

For increasing the intracranial pressure, an apparatus similar to

¹ From the Department of Neuropathology, Harvard Medical School.

that used by Cushing was employed. Ringer's solution in a container was raised by means of a pulley and string to any desired height on a graduated pole. The pressure thus obtained was communicated to the intracranial cavity through a needle in the cisterna magna or through a tube whose outlet lay beneath the window over the parietal cortex. The Ringer's solution passed through a coil immersed in warm water so that only warmed fluid entered the cranium.

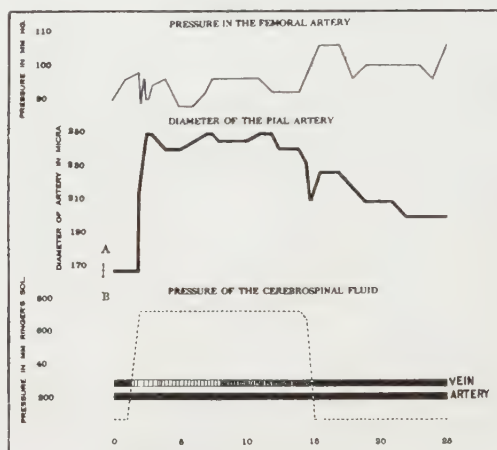


FIG. 35. Experiment 67. Sudden moderate increase in pressure. Weight of animal, 4 kilo. Anesthesia, 41 cc. amytal (intraperitoneally). The cerebrospinal fluid pressure was quickly (one minute) raised to a pressure of 750 mm. Ringer's and kept at that level twelve minutes. Within forty-five seconds the pial artery started to dilate and within another forty-five seconds it had dilated 47.3 per cent. The pial artery remained dilated during the intracranial pressure increase and then constricted coincident with the lowering of the pressure. The systemic arterial pressure changed but slightly during the entire experiment—the highest level reached was but 16 mm. Hg. above the initial. When the cerebrospinal fluid pressure first was at its height the flow in the veins was very slow. It later became more rapid.

The varying rates of blood flow, though not measured, were roughly estimated by noting the varying speed of red cells through any given vessel. This has been schematically represented at the bottom of the charts.

OBSERVATIONS

Twelve cats were used for these experiments. Although in the different animals some variations in response to high intracranial

pressure were seen, yet the usual sequence of events was as follows: until the cerebrospinal fluid pressure was raised to a height four or five times the normal no visible change in the pial vessels occurred; then as the pressure was increased there was noticed a slowing of blood flow through the veins, dilation of the veins, dilatation of the

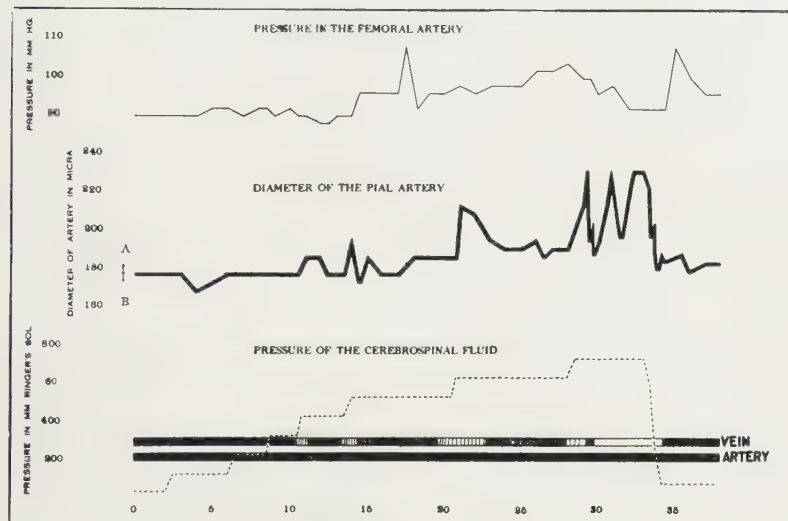


FIG. 36. Experiment 67. Slow moderate increase in pressure. Weight of animal, 4 kilo. Anesthesia, 41 cc. amytal (intraperitoneally). The cerebrospinal fluid pressure was slowly raised 100 mm. Ringer's about every two to seven minutes (total $28\frac{1}{2}$ minutes). The pial artery diameter with the exception of minor fluctuations changed little until 650 mm. pressure had been reached. It then momentarily dilated and immediately constricted as soon as the pressure was lowered to 100. During the experiment there were but minor variations in systemic arterial pressure. The greatest increase was 16 mm. Hg. when the intracranial pressure had reached 550 mm. Ringer's. No change in the arterial flow could be detected, but the venous flow slackened for a time after the last pressure increase and even stopped momentarily when the cerebrospinal fluid pressure was at 750 Ringer's. It was fairly constant and rapid between each elevation.

arteries, slowing of blood flow through the arteries, narrowing of the arteries and finally complete emptying of these vessels and blanching of the cortex.

The alterations in size of pial vessels and in the rate of flow (during periods of normal blood pressure) depended chiefly on two factors:

the extent to which the pressure within the skull was changed and the rapidity of the change. Raising the pressure abruptly (in one minute) to 750 mm. Ringer's resulted in a slowing of venous flow, dilatation of pial veins and a pulsating flow of blood corpuscles in the veins. The pial arteries promptly dilated (fig. 35) and stayed so

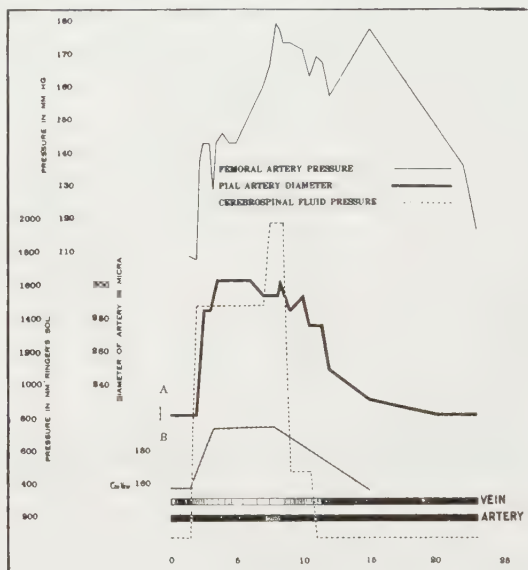


FIG. 37. Experiment 25. Sudden great increase in pressure. Weight of animal, 2.3 kilo. Anesthesia, 19 cc. amytal (intraperitoneally). The cerebrospinal fluid pressure was raised to 1500 mm. Ringer's solution in one-half minute and kept there five minutes before being further elevated 500 mm. The systemic arterial pressure rose and the pial artery started to dilate within one-half minute after the first increase in cerebrospinal fluid pressure. The artery dilated 36 per cent. The systemic arterial pressure was 71 mm. Hg. higher and maintained this level. The pial artery constricted while the blood pressure was still elevated. The changes in pial vein diameter roughly paralleled those of the pial artery. 10 per cent dilatation occurred. The flow in both artery and vein slowed when the cerebrospinal fluid pressure was at its height but returned to normal when it was lowered.

until the intracranial pressure was released, when they returned to their former size. As only minor fluctuations in systemic arterial pressure occurred at the time, the dilatation must have had some cause other than an increase in systemic arterial pressure. The probable cause of the dilatation will be discussed later.

Raising the intracranial pressure very slowly (in twenty-eight minutes) to the same height as before resulted in similar changes, but these came on more slowly and with a preliminary slight narrowing of the artery (fig. 36). The slowing of pial venous flow was observed in

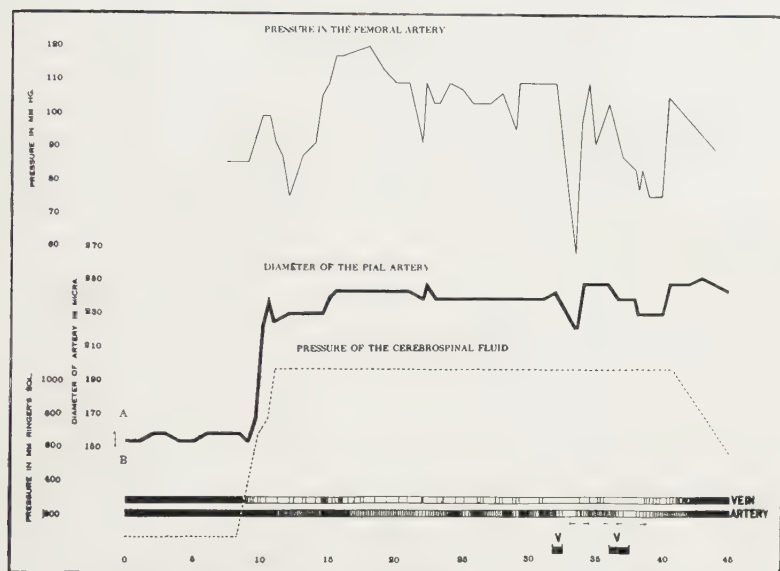


FIG. 38. Experiment 67. Effect of systemic arterial blood pressure variations. Weight of animal, 4 kilo. Anesthesia, 41 cc. amytal (intraperitoneally). The cerebrospinal fluid pressure was raised within two and three-fourths minutes to 1100. The pial artery at first constricted slightly and then dilated 50 per cent. The systemic arterial pressure rose. The cerebrospinal fluid pressure was held at 1100 for thirty-one minutes. The pial artery dilated slightly and remained fairly constant. Upon stimulation of the vagus nerves the systemic arterial blood pressure fell, and with the fall the pial artery constricted. During the period of great fall in blood pressure the flow in the artery stopped and reversal occurred. (Arrows indicate direction of flow.) Note the relationship between arterial flow and systemic arterial pressure. The venous flow was also impaired throughout the period of pressure increase and stoppage occurred with cessation of arterial flow.

all cases, regardless of whether the pressure were raised suddenly or slowly. Soon after the arteries dilated the venous flow, although still slower than normal, began to increase its rate (*i.e.*, the cerebral circulation was becoming adjusted, even though the intracranial pressure was steadily maintained at an abnormal height). When the pressure

was lowered to 100 mm. Ringer's there followed immediately a further increase in rate of venous flow and a prompt narrowing of arteries and veins (figs. 35-36).

If the pressure were raised to a greater height (1500 to 2000 mm. Ringer's), in one-half to one minute the changes already described

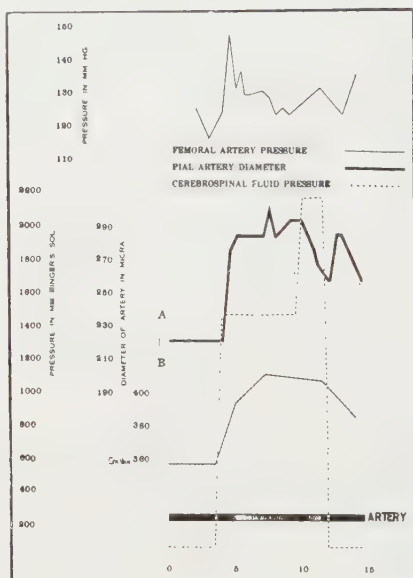


FIG. 39. Experiment 25. Venous and delayed arterial dilatation. Weight of animal, 2.3 kilo. Anesthesia, 19 cc. amytal (intraperitoneally). The cerebrospinal fluid pressure was raised in one-half minute to 1500. The pial vein immediately dilated but the pial artery did not until shortly after (dilatation 28 per cent). The systemic arterial pressure immediately rose 31 mm. Hg. The cerebrospinal fluid pressure was raised to 2200. The systemic arterial pressure immediately rose slightly, the pial artery constricted and the arterial flow slowed. When the cerebrospinal fluid pressure was lowered the systemic arterial pressure fell, and whereas the blood pressure was lower than the initial level, the pial artery dilated. Note the relation between systemic arterial blood pressure, the arterial flow and pial artery diameter during increase in intracranial pressure.

were soon followed by emptying of some of the pial veins, by a rise in systemic arterial pressure and by further dilatation and slowing of flow in pial arteries (figs. 37, 39, 41). When the intracranial pressure was suddenly released the pial arteries, which had begun to show

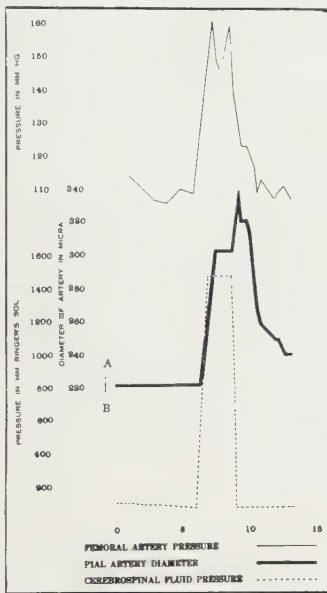


FIG. 40

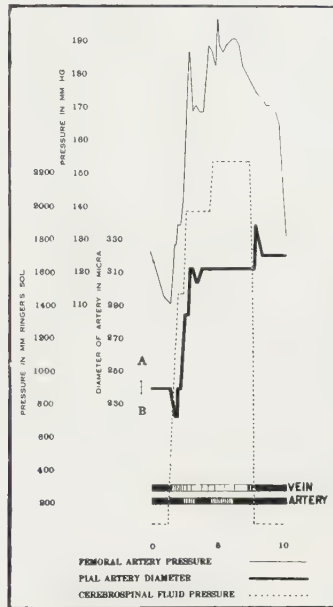


FIG. 41

FIG. 40. Experiment 28. Delayed arterial dilatation. Weight of animal, 3.1 kilo. Anesthesia, 30 cc. amytal (intraperitoneally). The cerebrospinal fluid pressure was raised in one minute to 1500 mm. Ringer's solution. The pial artery dilated 36 per cent and the systemic arterial pressure rose 86 mm. Hg., the pial artery constricted slightly and then dilated 29.6 per cent. When the cerebrospinal fluid pressure was lowered it further dilated 8.5 per cent. The dilatation in this instance was associated with elevation in blood pressure. The flow in both artery and vein was appreciably lessened during the height of intracranial pressure increase but regained its natural speed when the pressure was again at 100.

FIG. 41. Delayed arterial dilatation after a period of increased arterial flow. The animal weighed 3.1 kilo. It was anesthized with 30 cc. of 1 per cent iso-amyl-ethyl barbituric acid, injected intraperitoneally. The cerebrospinal fluid pressure was raised to 2,200 mm. of Ringer's solution in seventy seconds, and held at this pressure for two minutes before a final elevation of 300 mm. When the intracranial pressure was first raised, the systemic arterial pressure rose 86 mm. of mercury, the pial artery became narrower and then dilated 29.6 per cent. When the cerebrospinal fluid pressure was lowered, it further dilated 8.5 per cent. The dilatation in this instance was associated with elevation in blood pressure. The flow in both artery and vein was appreciably lessened during the height of the increase of intracranial pressure but regained its initial speed when the pressure was again at 100 mm.

slight cyanosis, dilated still more and became bright scarlet, and the veins—previously purple—now approached the arteries in color and became dilated also and filled with blood, flowing at a very rapid

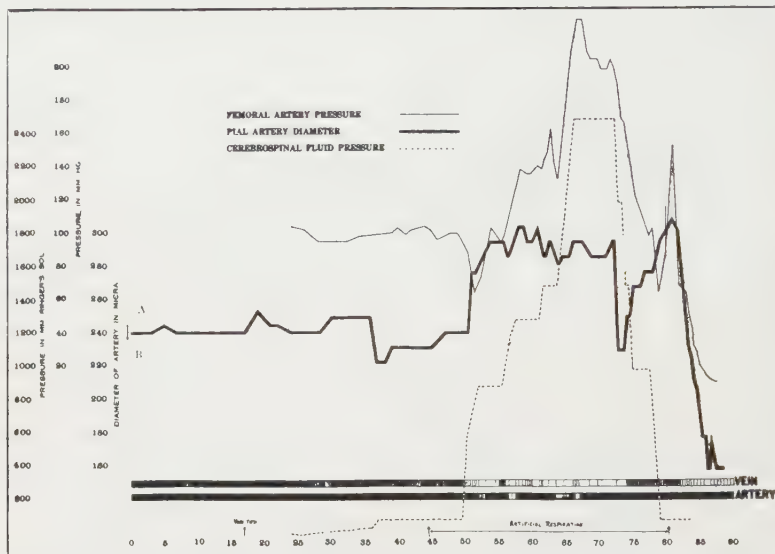


FIG. 42. Experiment 35. Weight of animal, 3.1 kilo. Anesthesia, 25 cc. amytal (intraperitoneally). After tying the vagus nerves the cerebrospinal fluid pressure was gradually raised to 2500. The artery immediately dilated and remained so (approximately 22 per cent). After the cerebrospinal fluid pressure had been at 2500 mm. Ringer's for several seconds the systemic arterial pressure rose to 230 mm. Hg. With blood pressure fall, the circulation in the pial artery became slower and the vessel constricted. The cerebrospinal fluid pressure was lowered. Pial artery dilatation continued in spite of the sharp drop in blood pressure, and was almost maximal when the blood pressure was lowest. The venous flow was slow from the onset of the intracranial pressure increase and stopped when the arterial flow stopped. Note the relation between the pial artery diameter and venous flow in the first part of the pressure increase; between artery diameter and systemic blood pressure when the intracranial pressure was elevated; between impaired circulation and delayed dilatation after intracranial pressure had been reduced to normal.

pace (figs. 40, 41). It was ten or fifteen minutes before the arteries regained their original sizes (fig. 37).

Supposing, however, the intracranial pressure were held at a high level (1100 mm. Ringer's) for a longer period (thirty minutes). If a

sharp fall in arterial pressure was caused by stimulation of the peripheral end of the cut vagus nerve, there resulted a narrowing of pial arteries, a slowing, then cessation of flow in veins and arteries, and sometimes even a momentary reversal of flow in the latter. When the arterial pressure returned to its former level the flood flow and caliber of vessels followed suit (fig. 38).

The caliber of the pial arteries, thus, varied in the same direction as the systemic pressure, or if this were constant it varied directly with the intracranial pressure (figs. 36, 42). As mentioned above, under these conditions (increased intracranial pressure for a long period) a fall in systemic arterial pressure of 60 mm. Hg (fig. 38) caused a decided reduction in diameter of the pial artery.

Under normal intracranial pressure, on the other hand, the diameter of the pial artery was relatively independent of changes in systemic arterial pressure. Only great fluctuations in the latter—over 60 mm. Hg—affected the caliber of the artery, and often a moderate fall in arterial pressure was observed while the pial artery was dilating, and vice versa. This has been noted repeatedly (5).

The speed of blood flow, too, through the pial vessels was chiefly controlled not by the arterial pressure alone, but by the ratio of cerebral arterial to intracranial pressure (or more exactly intracranial venous pressure, which is usually very close to it). When both these pressures were normal the flow in a pial artery, 180 microns in diameter, was so rapid that no movement of the blood corpuscles within the artery could be detected. It was not until the arterial pressure fell to 20 mm. Hg. or lower, that the flow slowed sufficiently to become visible. When, however, the intracranial pressure was very high the corpuscles in the same artery could be seen if the arterial pressure fell only to 60 mm. Hg. In all cases of retarded flow the corpuscles were seen first in the smaller vessels. When the intracranial pressure was normal reversal of flow in the arteries did not occur till the heart failed. Then the blood flowed from the head, where the pressure was about 50 mm. Ringer's, into the chest where it was slightly lower. Soon the arteries became empty and somewhat narrowed, but not collapsed. If, however, the intracranial pressure was negative (less than atmospheric) when the heart failed, then the pial arteries dilated and remained filled with blood.

Under normal or low intracranial pressure a striking thing was noticed in every animal in which, from any cause, the respiration and

circulation failed. When the systemic arterial pressure fell below 10 mm. Hg., and the circulation even in the larger arteries of the pial began to slow, and the corpuscles became more and more cyanotic, then the slightest compression of the thorax, as in gentle artificial respiration, caused a remarkable set of changes. Instantly the stagnant corpuscles in the half-filled arteries began to flow forward rapidly in the normal direction; within three or four seconds the corpuscles in all the visible arteries turned from lilac to scarlet, and the arterial flow temporarily, at least, was reestablished. This gave a vivid illustration of the promptness with which, in asphyxia, artificial respiration brought relief.

COMMENT

To maintain cerebral circulation during periods of increased intracranial pressure it seems that at least three important physiologic mechanisms are involved.

First, the following adjustment probably occurs: the increased pressure of the cerebrospinal fluid is transmitted readily to the interior of the thin-walled veins, in which the pressure is relatively low. Thus the intracranial venous pressure is raised and the blood flow retarded. The rise in pressure in the veins is transmitted to the capillaries and then to the arterioles, raising the pressure in each. There results an increase in arterial pressure within the skull, and there is established a slower, yet effective circulation through the brain, without any rise in systemic arterial pressure.

Second, in response to cerebral anemia, when the first adjustment is no longer adequate, there occurs a rise in pressure in the systemic arteries.

Third, a factor (which must assist the other two) is the reduction in vascular tone, or relaxation of the vessel walls associated with asphyxia. Thus, dilatation is favored and a greater volume of blood can flow through the cerebral vessels with less resistance than before.

Evidence for the first physiologic mechanism described is to be found in experimental and in clinical observations. Fleming and Naffziger (6) in dogs measured the pressure in the Circle of Willis by introducing a cannula into the cranial end of the ligated carotid artery. Then they partially stopped the other cerebral arteries. After constant pressure and volume flow had been established the experimenters stopped the venous outflow. The last procedure raised

the pressure in the Circle of Willis. It seems reasonable to conclude that this rise in pressure resulted from a sudden increase in venous pressure transmitted through the capillaries to the arterioles and through them to the larger arteries at the base of the brain.

Baillart and Berens (7) measured the pressure in the retinal artery in man and concluded that there was increase in retinal arterial pressure in patients with increased intracranial pressure. In these cases there was no increase in pressure in the systemic arteries.

A rise of arterial pressure locally within the cranium, in the presence of increased intracranial pressure, is of the utmost importance. It explains on a mechanical basis both the experimental observation that intracranial pressure may be raised to levels approaching the systemic arterial pressure without shutting off the cerebral circulation, and the clinical observation that patients with high intracranial pressure of gradual development (notably brain tumors) can have functioning cerebral circulation together with normal systemic arterial pressure. The "Cushing phenomena" occur clinically only when the intracranial rise is sudden and very marked, as in intracranial injury or in terminal stages of expanding lesions.

It has been mentioned that after release of high intracranial pressure the dilated pial artery became still wider. The explanation of this by Cushing (3) was that the sudden removal of the supporting extravascular pressure allowed the arterial pressure—still high—to push out the vessel walls. Possibly several additional factors contribute to the same end. One of these has been already mentioned. This is the relaxation of vessel walls or loss in vascular tone which occurs after partial asphyxia, from any cause (8). The cause of asphyxia here is the greatly retarded blood flow through the pial vessels. Great dilatation, also, of the pial arteries has been observed after clamping the common carotids (9). Inhalation of air or oxygen to which were added varying percentages of carbon dioxide brings about the same result (10).

SUMMARY

Alterations in rate of blood flow through the cerebral vessels depends on the ratio of cerebrospinal to systemic arterial pressure (or, more truly, of intracranial venous to intracranial arterial pressure). The greater the difference in pressure the more rapid the flow.

When intracranial pressure is raised to a great height the following

changes in pial circulation take place: slowing of the blood flow and dilatation of the veins and of the arteries. Finally, when the pressure becomes great enough to stop the cerebral circulation, the arteries become narrow and empty.

Circulation through the cerebral vessels is maintained at moderately increased intracranial pressures without any rise in systemic arterial pressure. It is accompanied by dilatation of cerebral arteries and may be accounted for as follows: the rise in pressure of the cerebrospinal fluid raises the pressure in the capillaries, in the arterioles, and in the smaller arteries, causing dilatation of all these vessels.

When the intracranial pressure is raised to a still greater height the cerebral circulation begins to fail. The systemic arterial pressure then rises and the circulation of the brain is reestablished. This compensation may occur several times, if the intracranial pressure is raised by steps.

Sudden release of high intracranial pressure brings about great dilatation of pial arteries, probably largely owing to relaxation of their walls; this, in turn, is due to partial asphyxia from the previous slowing of the cerebral circulation.

DISCUSSION

The following question submitted to Dr. Wolff before the Commission, together with the answer to it, is here reported verbatim.

DR. L. F. BARKER: I note that Dr. Wolff speaks of the change in the vasomotor tone in the pial vessels as being in opposite direction to the vasomotor tone in the systemic vessels.

DR. H. G. WOLFF: It is difficult to determine which factor of several is *chiefly* responsible for the vasodilatation here described. The dilatation may result from a direct action upon the vessel wall of accumulated metabolites and defective oxygen supply or be the result of the action of similar abnormalities upon the vasomotor center. Our experiments permit us to draw no definite conclusions concerning the exact part played by each.

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CHAPTER VII

THE RELATION OF VASCULAR HYDROSTATIC PRESSURE AND OSMOTIC PRESSURE TO THE CEREBRO- SPINAL FLUID PRESSURE¹

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CERTAIN basic relationships of osmotic pressure and vascular hydrostatic pressure to the problem of fluid exchange across capillary walls in general and to the cerebrospinal fluid pressure in particular form the content of this paper.

In two recent articles by one of us (1), (2), the theories as to the nature of the cerebrospinal fluid have been reviewed and the conclusion reached that the cerebrospinal fluid is formed by a process of dialysis or filtration from the arterial blood in the capillaries of the choroid plexus and is reabsorbed by a similar process into the venous blood of the dural sinuses. In this process a delicately balanced equilibrium exists between the formation and the reabsorption of the cerebrospinal fluid and the osmotic and hydrostatic pressures of the arterial and venous blood, by virtue of which the normal cerebrospinal fluid pressure is maintained.

The ideas to be explained in this paper are an elaboration of the mechanisms involved in this equilibrium and are based upon the acceptance of the above view of the nature of the cerebrospinal fluid.

A quantitative description of the factors maintaining and influencing intracranial pressure must await further data concerning the rate and volume of cerebral blood flow, the capillary pressures within the brain and choroid plexus, the exact osmotic relationships between cerebral arterial and venous blood, and the partial osmotic pressure due to plasma proteins and other substances to which the capillary walls may be impermeable. The direction, however, in which these factors influence fluid exchange is sufficiently well known to permit of qualitative analysis.

The cerebrospinal fluid may be described as a protein-free dialysate in hydrostatic and osmotic equilibrium with the plasma, ("Dialysat

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équilibrée"-Mestrezat) (3). The normal cerebrospinal fluid contains practically no protein and no lipoids. All the inorganic salts and readily diffusible organic substances of the plasma, however, are found in aqueous solution. The cerebrospinal fluid has essentially the same osmotic pressure and hydrogen ion concentration as the plasma.

We wish here to emphasize the fact that the above description of the cerebrospinal fluid² applies equally to the known properties of the "true lymph" or intercellular fluid which bathes the tissue cells. Here also a protein-free fluid filters through the arterial portion of the capillary-wall under the influence of the higher capillary pressure and is reabsorbed into the venous portion of the capillary bed where the hydrostatic pressure is less than the opposing osmotic effect of the plasma proteins. This theory of the mechanism for fluid exchange—Starling's greatest contribution to physiology (6)—has received important support in the quantitative studies of Landis (7), to which we shall return. With these considerations in mind it becomes evident that *the formation and absorption of the cerebrospinal fluid is but a special example of the general mechanism of fluid exchange between capillary blood and tissue spaces throughout the organism—a mechanism whose maintenance and proper regulation is the only function of entire circulatory and pulmonary apparatus.*

Before we can hope to understand the special problem within the cranium it is essential to have clearly in mind those factors which throughout the organism dominate fluid exchange between capillary blood and tissue spaces. These can be reduced to three: the character of the semipermeable membrane, osmotic pressure, and hydrostatic pressure. Specifically, we have to deal with the character of the capillary wall, and the relative hydrostatic and osmotic pressures on either side of this wall. It is our purpose to review the most important influences which may modify these three factors in fluid exchange:

THE MEMBRANE

With certain notable exceptions, such as the liver, fluid can escape from the plasma only by passing through the endothelial membrane forming the wall of the capillaries. To this extent the membrane is the same in the brain and in most parts of the body. In the choroid plexus to be sure there is another layer of cells, the modified ependy-

² The aqueous humor of the eye is almost identical with the cerebrospinal fluid "Mestrezat 1912" (3) and has the same relationship to the plasma (W. S. Duke-Elder, *The Nature of the Intraocular Fluids* (4)). The glomerular urine presents a close analogy. (Wearn, and Richards (5)).

mal cells covering the choroid plexus, through which the fluid must pass before it reaches the ventricles. It is not reasonable to suppose that such an additional layer of cells may not modify the character of the fluid, and indeed there is evidence (Stern (8)) to show that certain foreign substances at least will pass through the capillary wall in the general circulation, but will not enter the cerebrospinal fluid. Nevertheless, granting that local differences in permeability undoubtedly exist, there is common to the capillary wall membrane throughout most of the body the fact that it is composed of a single layer of endothelial cells, and that this endothelial wall is normally impermeable to protein, but freely permeable to water, oxygen, carbon dioxide, glucose, amino acids, urea, sodium chloride and so forth. For the purposes of this discussion of the factors dominating fluid exchange, we want to call attention to this common property of the membrane—that it is impermeable to protein, but freely permeable to nearly all the other substances dissolved in the plasma in sufficient concentration to influence osmotic pressure.³

With capillary dilatation, the wall becomes thinner, and vice versa. This is the only change known to occur normally in the character of the membrane with which we are dealing. As this dilatation of the capillary, and thinning of the capillary wall, within physiological limits, does not modify its impermeability to protein (Landis (9)) we may proceed on the basis that the capillary wall, both within the cranium and throughout the tissues in general remains normally impermeable to the proteins and freely permeable to practically all the other osmotically active substances present in the plasma.

THE OSMOTIC PRESSURE

If pure water be separated from an aqueous solution of glucose by a membrane which is freely permeable to the water but impermeable to glucose, water will pass across the membrane into the glucose solution tending to dilute it. This process is called osmosis. If, however, enough external pressure be applied to the glucose solution the passage of water into it can be prevented. That pressure, just sufficient to prevent the movement of water into the glucose solution, is numerically equivalent to the osmotic pressure of the solution.

The ultimate cause of osmosis is intimately related to the phenomenon of solution. A discussion of the theories involved is beyond

³ In the ultimate analysis, however, it must be recognized that local differences in permeability, in the various tissues, may have great physiological importance.

the scope of this paper. Since osmosis plays an essential part in every life process, and since fluid exchange in general and intracranial pressure in particular may be completely dominated by changes in the osmotic pressure of the blood, a statement of the facts of osmosis is necessary to an understanding of intracranial pressure. A non-mathematical visualization of the process in the simplest terms consistent with accuracy should be useful in proceeding from the laboratory of physical chemistry to the clinical problem of intracranial pressure.

If a pig's bladder, permeable to water but not to glucose, be filled with glucose solution and immersed in water, water will diffuse into the bladder and cause it to swell and the pressure within it to rise. There are several ways of visualizing this process: one, that the molecules of glucose by bombardment of the inner surface of the elastic bladder actively distend it, the entrance of water from without being wholly passive. This is the familiar explanation offered in most of the text-books on physiology. It is consistent with the fact that the degree of pressure developed is almost exactly proportional to the number of glucose molecules in solution. The bombardment theory, however, fails to give an adequate explanation for the passage of water across the membrane into the glucose solution when the membrane is rigid and no distention can occur. With such a membrane a pressure of 9200 mm. of mercury would have to be exerted upon a 10 per cent glucose solution to prevent the passage of water into it.

The underlying principle in an alternative method for visualizing the phenomenon of osmosis is that the energy which manifests itself as osmotic pressure is inherent in the pure solvent (water) outside the membrane, not in the solute (glucose) inside.

The molecules of any liquid tend to escape from the surface of the liquid into the atmosphere or gas phase above the liquid. This is the cause of vapor tension. This tendency for the molecules to escape is a fundamental property of all liquids and is the basis of osmosis. It is increased by raising either the temperature of a liquid or the pressure to which the liquid is exposed. The tendency for molecules to escape from the surface of a liquid is *greatest when the liquid is pure*, and is *diminished* by the presence of any substance dissolved in the liquid. If glucose or sodium chloride for instance be dissolved in water, the tendency for molecules of water to escape is diminished, *i.e.*, the vapor tension of the solution is lower than that of pure water.

Moreover, this decrease in the tendency for molecules of water to escape from the surface applies not only to the surface exposed to a

gas, but also to the surface exposed to any membrane which is permeable to the water molecules. It has been found that the amount of this decrease in the tendency for molecules to escape is directly proportional to the total number of particles, molecules and ions, dissolved in the pure liquid (*ie.*, every molecule of sodium chloride which dissociates into two ions, Na^+ and Cl^- produces twice the effect of the single undissociated molecule of sodium chloride). As osmotic pressure is also directly proportional to the total number of molecules and ions in solution, the osmotic pressure of a solution may be defined as the measure of *decrease* in the tendency for molecules of the pure solvent to escape from the surface of a solution (either into a gas phase or across a semipermeable membrane) due to the presence in solution of some dissolved substance. It has been found that a simple mathematical relationship exists between the osmotic pressure, the vapor tension, the boiling-point and the freezing-point of a solution, such that if any one of these be known, the value of the others can be calculated directly therefrom.

With these factors in mind the mechanism of osmosis may be visualized as follows: if a membrane permeable to water separate two portions of pure water from one another, the tendency for molecules of water to cross the membrane in one direction is exactly balanced by the opposing tendency in the other direction and no movement of water as a whole will occur (provided that the temperature and hydrostatic pressure be equal on the two sides of the membrane). If now pure water be separated from an aqueous solution of glucose by a membrane permeable to water but not to glucose, it will be seen that water as a whole must move across the membrane into the glucose solution, because, owing to the presence of the glucose molecules in the water on one side, the tendency for molecules of water to escape from the surface of the glucose solution across the membrane into the pure water on the other side has become *decreased*, and no longer balances opposing tendency in the opposite direction. In other words, the escaping tendency of water molecules from the pure water into the glucose solution, while unchanged in actual amount, is now relatively greater than that from the glucose solution into the pure water.

Osmotic pressure then is the measure of the *decrease* in tendency of molecules of a solvent (in biology, water) to escape from the surface of a solution as compared to their tendency to escape from the surface of the pure solvent. The *total osmotic pressure* of a solution is the measure of the total decrease in this tendency to escape due to the

sum of all the molecules and ions present in the solution, whereas the *partial osmotic pressure* due to one constituent in a solution is the measure of that fraction of the decrease in the tendency for molecules of the solvent to escape due to the presence of the particular constituent in question. The *total osmotic pressure* of the blood plasma is about *five thousand four hundred millimeters* of mercury—that is, if a membrane were to separate plasma from pure water, and were impermeable to everything in the plasma except water, a hydrostatic pressure equivalent to a column of mercury more than 5 meters high would have to be exerted upon the plasma to prevent the passage of water across the membrane into it.⁴ The partial osmotic pressure due to the glucose normally present in plasma (100 mgm. glucose per 100 cc.) is more than 90 mm. of mercury, whereas the osmotic pressure of the plasma proteins, the only osmotically important substance to which the capillary wall is known to be impermeable, is equal to only 20 to 30 mm. of mercury, less than 1/200 of the total osmotic pressure of the plasma.

In the cranium, as well as in the eye, where volume changes are limited, variations in the relative osmotic pressure of blood and cerebrospinal fluid are reflected chiefly as changes in intracranial or intraocular pressures (Weed (11), Duke-Elder (4)), whereas in tissues not rigidly confined, volume changes, *i.e.*, edema or dehydration, result.

THE HYDROSTATIC PRESSURE

The only way in which the vascular hydrostatic pressure can influence fluid exchange is by changing the relative pressures on the inside and outside of the capillary wall. In the tissues which are not rigidly confined, the outside pressure approximates the atmospheric pressure and will not be modified directly by variations in the volume of arterial or venous tree. It follows that the only way in which arterial or venous blood pressure can influence fluid exchange is by their influence upon capillary blood pressure. In the cranium, however, volume changes in arteries or veins will affect intracranial volume and hence cerebrospinal fluid pressure directly. Thus the vol-

⁴ No membrane has been made to withstand such a pressure. Other methods must be used to determine such osmotic pressures. The raising of the boiling-point, the depression of the vapour tension and the depression of the freezing-point of a solution are all directly proportional to the total osmotic pressure of the solution—this has been verified experimentally—and one of these methods is commonly used.

ume increase of the cerebral arterial tree (dilatation and elongation) produced by each cardiac systole causes in man a rise in cerebrospinal fluid pressure of about 2 mm. of water (measured in the horizontal position with a 1 mm. bore standpipe manometer). Similarly the immediate rise in intracranial pressure upon jugular compression as well as the slight rise and fall accompanying normal expiration and inspiration are the results chiefly of volume changes in the cerebral venous system.

THE CAPILLARY PRESSURE

The only direct measurements of human capillary pressure are those of Carrier and Rehberg (12), carried out in Krogh's laboratory. The pressure in the venous limbs of capillary loops in the skin at the base of the finger nail was measured directly by inserting a capillary pipette and balancing the capillary pressure with a column of saline solution. The pressures obtained in the hand held at any level above the clavicle varied from 45 to 75 mm. of water (approximately 3 to 5.5 mm. Hg.). It is probable that the pressure in the arterial limb of the capillary is slightly greater than this, for Landis has shown by similar measurements in the mesentery of the frog and cat a gradient of pressures fall from the arterial to the venous side of the capillary bed. It is also probable that the pressures in the capillaries investigated by Carrier and Rehberg (12) are minimal, because the skin capillaries at the base of the nail are relatively large. Nevertheless, these values serve to emphasize the fact that capillary pressure is extremely small compared to arterial pressure. In the cranium the capillary pressure is somewhat higher, for it must be greater than cerebrospinal fluid pressure, else the latter would obliterate the capillaries. The normal intracranial pressure in the horizontal position varies from 80 to 180 mm. of water, averaging about 130 mm.

THE INFLUENCE OF ARTERIAL PRESSURE UPON CAPILLARY PRESSURE

Many misconceptions have arisen through expressing related values in different terms; *i.e.*, arterial pressure in millimeters of Hg. and venous or cerebrospinal fluid pressure in millimeters of water. To bring the pressure relationships into sharp relief, and because spinal fluid pressure is best expressed in millimeters of water, all pressure values will be so expressed in the remainder of this paper.

The normal arterial pressure of 120 mm. Hg. systolic and 80 mm. Hg. diastolic will now become approximately 1600 mm. of water systolic,

and 1100 mm. of water diastolic; the pulse pressure of 40 mm. Hg. will be 500 mm. of water and the capillary pressure from 45 to 75 mm. of water. The venous pressure will be somewhat less than the capillary pressure (Carrier and Rehberg (12)). If there were not a pressure gradient from capillary to vein, no flow of blood could occur.

We may now visualize the system—the arterial pressure in diastole at 1100 mm. of water, rising with each heart beat 500 mm. to 1600 mm. of water—the average capillary pressure at or above the level of the heart not far from 100 mm. of water and *not varying appreciably* with the heart beat, while the venous pressure is always somewhat lower than the capillary pressure.

In passing from larger arteries to capillaries this marked drop in pressure, *i.e.*, from 1600 mm. to 100 mm. of water occurs chiefly in the arterioles which are both narrow individually and have but a small total area of cross-section compared to that of the capillaries, *i.e.*, each arteriole feeds a group of capillaries. The arterial pulse is transmitted to the arterioles, but is lost when the capillaries are reached. The absence of any measurable variation in capillary pressure resulting from the increase in arterial pressure of 500 mm. of water with each systole is most convincing proof that *marked variations in arterial blood pressure can and do occur without appreciably influencing the capillary pressure.*

THE INFLUENCE OF VENOUS PRESSURE UPON CAPILLARY PRESSURE

The situation here is quite the reverse of that in regard to arterial pressure, for there are no narrow arterioles between the veins and the capillaries, and an intimate pressure correlation exists between them. (The valves in the veins are only effective when closed, *i.e.*, when complete cessation of flow occurs.) The far greater influence of venous pressure changes than of arterial pressure changes upon capillary pressure was recognized by Carl Ludwig and insisted upon by Leonard Hill (13). Direct proof is furnished by the measurements of Carrier and Rehberg (12), who have shown that the capillary pressure in the human hand and foot bears a constant relationship to the venous pressure of the part, both capillary and venous pressures varying directly with the height of the part relative to the thorax.

This means that although *a pressure change of 500 mm. of water in arterial pressure produces no appreciable change in capillary pressure, a variation of 10 mm. of water in venous pressure changes the capillary pressure in the same direction to almost exactly the same degree.*

THE VASCULAR TONE

In addition to the venous pressure, there is one other important influence upon capillary pressure—the vascular tone. Since the arterioles are the point of greatest resistance to blood flow (*i.e.*, the greatest fall in pressure gradient occurs here) the degree of contraction of these vessels not only maintains the high level of arterial pressure, on the one hand, but also regulates the amount of arterial pressure which is transmitted to the capillaries. It will be seen that *variations in the caliber of the arterioles influence arterial and capillary pressures in diametrically opposite directions*, for if the *arterioles dilate*, thus decreasing the peripheral resistance to blood flow, the *arterial pressure must fall*, but the *capillary pressure will rise* (and also venous pressure) since the arterial is more directly transmitted to the capillaries (and veins) through the now dilated arterioles. The rate of blood flow and the return of the blood to the heart will also be increased. Conversely, *if the arterioles constrict*, increasing the peripheral resistance, the *arterial pressure will rise*, but since less of this pressure can reach the capillaries, the *capillary (and venous) pressure must fall*. At the same time the damming back of the blood by the constricted arterioles decreases the rate of blood flow and the return of blood to the heart.

This mechanism must, however, be followed a step further, because vasomotor phenomena are usually limited to a certain area of the total vascular bed, and we have described those changes only which occur to the affected area. The passive changes occurring in other areas are also of great importance.

During vasomotor changes in the splanchnic area let us follow the purely passive changes in arterial, capillary and venous pressure resulting in other parts of the body, *i.e.*, a limb, where we shall assume a constant vasomotor tone. If there is vaso-constriction (*i.e.*, arteriole constriction) in the splanchnic area, the effect upon the arterial pressure will be in the same direction as if there was a generalized constriction of arterioles. The general arterial pressure, both systolic and diastolic will rise, throughout the organism. What will be the effect upon capillary pressures in the limb? We have shown above that rather marked changes in arterial pressure produce little change in capillary pressure directly, so if the arterioles in the limb maintain their original tone the general arterial pressure rise should have little if any direct effect upon this local capillary pressure in the limb. The venous pressure in the splanchnic area has been markedly diminished by the local vaso-constriction, the venous return to the heart diminished, and the general venous pressure will inevitably fall. A change

in venous pressure we have shown is reflected nearly quantitatively in the capillaries. Hence, the capillary pressure in the limb would tend to fall about equally with the fall in general venous pressure, and would not be appreciably affected by the rise in arterial pressure. Since a fall of a few millimeters of water in venous pressure is reflected nearly quantitatively in the capillary pressure, while an increase of 50 per cent of the arterial pressure may produce no appreciable change in capillary pressure, we must conclude that *the passive response in a limb to a local splanchnic vaso-constriction would be a rise in arterial pressure, a fall in venous pressure and a resulting fall in capillary pressure.*

Vaso-dilatation in the splanchnic area will produce opposite effects. The total resistance to blood flow is decreased, and the arterial pressure both locally and generally must fall; but with the decreased peripheral resistance in the splanchnic area the capillary pressure and venous pressure there will be increased, and this local increase in venous pressure will raise the general venous pressure. The capillary pressure in the limb will follow this general venous pressure rise far more directly than it will the fall in arterial pressure. (The above discussion of vasomotor phenomena does not claim to represent conditions actually obtaining in the organism, for these are nearly always more complicated. Such simplification, however, is necessary as a background for discussion and visualization of the hydrodynamics involved.)

ADRENALINE

The effects of adrenaline upon the vascular pressures are so important, and the results have been so much debated, that it is worth while to consider the action of adrenaline in the light of the above discussion. It is generally accepted, and undoubtedly true, that an effective dose of adrenaline produces vaso-constriction in the splanchnic area. The following considerations will show that such vaso-constriction alone cannot explain the observed facts.

Vaso-constriction, an increase in heart rate, and an increase in cardiac output per beat are established effects of adrenaline. Vaso-constriction must raise the blood pressure—both the systolic and diastolic pressure. It is well known, however, that after small doses of adrenaline, in spite of a rising systolic pressure, the diastolic pressure often *remains constant* or may even *fall*. (With large doses of adrenaline the diastolic pressure may also rise, but the increase in pulse pressure regularly occurs.) Were the heart rate slowed, or its

output per beat diminished, such a fall in diastolic pressure might be explained, but in the presence of an increased heart rate and increased output of the heart per beat (*i.e.*, an increased circulation rate) vaso-constriction alone cannot explain a falling or constant diastolic blood pressure. Moreover, the marked increase in circulation rate demands an increased return of blood to the heart, and an increased venous pressure. These effects cannot be explained by a vaso-constriction or increase in total peripheral resistance of the vascular system. A vaso-dilatation must occur in other parts of the body, and it must be greater in extent than the area of vaso-constriction if a constant or falling diastolic pressure is to be explained in the presence of a rising systolic pressure and a greater minute-volume output of the heart. The observed concentration of the plasma protein following adrenaline injections is thus readily explained as due to increased filtration from the capillaries in the area of vasodilatation where capillary pressure will be increased. In other words, the observed effects of adrenaline in the special condition above described are more consistent with a *decrease* than with an *increase* in the total resistance to blood flow—such a decrease producing a falling diastolic pressure or maintaining it constant in face of a greater cardiac output. The *rise in systolic pressure under these circumstances is to be ascribed not so much to the splanchnic vaso-constriction* (for this must be more than compensated by vaso-dilatation elsewhere) as to the *increased output of the heart*. This would produce just the effects observed; *i.e.*, a rising systolic pressure and a constant or falling diastolic pressure in the presence of a decreased total peripheral resistance to blood flow. An increase in the rate of flow and pressure in the large capillary bed of the muscles of the body including the heart, due to relaxation of arterioles feeding these capillaries would fit in with Cannon's (14) conception of the action of adrenaline as an adaptive emergency mobilization of the forces of the organism for action. Such a dilator effect of adrenaline upon the arterioles of voluntary muscle has been demonstrated.

The effect of adrenaline upon the circulation in an area of the body where the response is passive may now be considered. The general rise in venous pressure due to the increased blood flow through dilated arterioles in the muscles would *increase* the resistance to venous and capillary outflow (as well as the venous and capillary pressure) from an area where no vasomotor changes took place. These effects would probably more than offset the effect of the increased systolic pressure. In other words, in the area of vasodilatation the capillary pressure and venous pressure are increased because of greater blood flow

through dilated arterioles, while in the area which follows these changes passively, the venous pressure and the capillary pressure are raised passively due to a backing up of blood from the raised general venous pressure, and the rate of blood flow is decreased. It follows that the minute-volume of *blood flow through the area responding by active constriction of arterioles would be decreased; in the area where there is active dilatation of the arterioles the rate would be increased; while in an area responding passively the rate of flow would be decreased.* Only if the vaso-constriction produces a fall in venous pressure which balances the venous pressure rise due to vaso-dilatation elsewhere, *i.e.*, only when the general venous pressure remains constant or falls, can adrenaline produce an increased rate of blood flow through an area which responds passively.

These considerations may not be neglected in considering the effect of adrenaline upon the cerebral circulation, for a *passive response will generally mean a decreased blood flow and an increased intracranial pressure. An increased blood flow associated with an increased intracranial pressure can occur only if accompanied by active cerebral vaso-dilatation.*

FLUID EXCHANGE

As long as the composition of the plasma remains constant, the direction of fluid exchange across the capillary wall depends upon the balance between the hydrostatic capillary pressure and the partial osmotic pressure of those substances which cannot pass through the capillary wall.

Since the capillary wall is permeable to practically all osmotically active substances present in the blood except protein, we need consider only the osmotic pressure due to the plasma proteins, since all other substances will depress the tendency for water molecules to escape across the membrane equally in both directions.⁵ Thus there

⁵ This is not strictly accurate because of the so-called "Donnan effect" (15). At the hydrogen ion concentration of the blood, protein is a negatively charged ion combining with positively charged ions such as sodium. As the capillary wall is freely permeable to sodium, but not to the protein ion, there is produced an unequal distribution of the freely diffusible ions, such that the negatively charged ions are more concentrated on the protein free side of the membrane, and the positively charged ions more concentrated on the protein side of the membrane, *i.e.*, chloride ions are more concentrated in all dialysates in the body, including the cerebrospinal fluid, than in the plasma, while sodium is more concentrated in the plasma than in these protein poor fluids. The mathematical statement of these relationships is known as the Gibbs-Donnan Law. For the purposes of this paper, a quantitative treatment of the "Gibbs Donnan Equilibrium" is not necessary.

exists a delicately balanced equilibrium between the plasma proteins which decrease the tendency for water molecules to escape across the capillary wall into the tissue spaces, and the hydrostatic capillary blood pressure which increases this same tendency. When the depressing effect (*i.e.*, osmotic pressure) of the plasma proteins is overcome by a relatively high hydrostatic capillary pressure, water (and the diffusible substances dissolved in it) will move across the membrane, and fluid will accumulate in the tissue spaces. When the capillary pressure falls below the osmotic effect due to the plasma proteins, the reverse will take place. This is most readily illustrated in cardiac decompensation. When a limb is allowed to hang below the level of the heart, because of the high venous pressure the capillary pressure becomes higher than the osmotic pressure of the plasma proteins—and a nearly protein-free fluid leaves the capillary and accumulates as edema in the tissue spaces. If now the limb be raised above the level of the heart, the venous blood runs downhill towards the heart, the capillary pressure falls and the osmotic pressure of the plasma proteins, no longer overcompensated by the high hydrostatic pressure, becomes again effective, and fluid comes across the capillary wall from tissue space into the blood. The edema will rapidly disappear.

The delicacy of this balance is such that there is normally a tendency for fluid to filter from the blood into the tissue spaces from the arterial portion of the capillary where the capillary pressure is higher, and a tendency for fluid to be reabsorbed into the venous portion of the capillary where the hydrostatic pressure is lower. This is brought out strikingly by the experiments of Thompson (16) and his collaborators on the effect of posture upon blood volume. Thus we may visualize the capillary bed of the body as a vast filtering and absorbing system—fluid constantly escaping into the tissue spaces through the capillary wall in the arterial portion of the capillary bed and being reabsorbed again on the venous side of the capillary bed. The central nervous system, moreover, is no exception to this general statement, for here also the cerebrospinal fluid escapes from the arterial blood entering the choroid plexuses (across the capillary wall and

It must play a rôle in electrolyte distribution and fluid exchange wherever a membrane is permeable to some, but not to all of the ions. Such conditions are present throughout the organism, and in the ultimate analysis cannot be neglected. The general statement, however, that the hydrostatic pressure in the capillaries, and the osmotic pressure due to the plasma proteins oppose one another in a delicately balanced equilibrium is true as a first approximation and adequate to the present discussion.

layer of choroid plexus cells) into the ventricles and is reabsorbed into the venous sinuses through the membrane of the arachnoid villi.

THE EFFECT OF TISSUE METABOLISM

Cellular metabolism affects the intercellular fluids largely by breaking up molecules such as glucose and amino acids into a larger number of smaller molecules such as lactic acid, and CO_2 —thus depressing the movement of water molecules across the capillary wall into the blood (*i.e.*, raising the osmotic pressure of the tissue fluids). This action then works in the same direction as the hydrostatic pressure in the capillaries (helps filtration into the tissue spaces) and opposes the action of the plasma proteins. It is not possible to estimate how large this cellular metabolism effect will be, but the greater the metabolism the larger the effect. This is one of the factors providing a greater fluid exchange for those cells which are in greatest activity.

THE EFFECT OF VARYING THE OSMOTIC PRESSURE OF THE BLOOD

This has been discussed in some detail in a previous communication by one of us (F.-S. (2)). Injecting hypertonic glucose, sodium chloride, urea, and so forth, intravenously into the blood stream immediately depresses the tendency for water molecules to escape into the tissue fluids, but the tendency for water to cross from tissue fluid into the blood is not affected (until the glucose, etc., has diffused across and is present in equal concentration in blood and tissue fluids)—the immediate result will be a rapid movement of water from tissue fluids, including the cerebrospinal fluid and intraocular fluid, into the blood. Diluting the blood with water will have the reverse effect. The forces involved when hypertonic or hypotonic solutions are injected are enormous compared to the effect of the plasma protein or capillary pressure. A 10 per cent glucose solution would have to be subjected to a pressure of a column of water, 130 meters in height, to prevent the passage of water into it through a semi-permeable membrane. The reason why the cells of the tissues are not ruptured by such pressures is that the body membranes are freely permeable to glucose, and a partial equalization of concentration takes place almost immediately by diffusion, so that such pressure gradients never develop.

To summarize: The factors involved in fluid exchange across the capillary wall are the nature of the membrane, the relative hydrostatic pressure and the relative osmotic pressures inside and outside the membrane. The membrane is permeable to all the osmotically

important dissolved substances in the plasma except protein, so that normally we are dealing with a balance between the osmotic effect of the plasma proteins tending to prevent movement out of the capillaries, and the capillary hydrostatic pressure tending to increase this filtration into the tissue spaces. The activity of the tissue cells raises the osmotic pressure of the outside fluid which favors filtration into the tissue spaces. Normally, these factors are so balanced that fluid filters into the tissue spaces from the arterial portions of the capillary bed, and is reabsorbed quantitatively into the venous portions of the capillary bed. Arterial blood pressure has relatively little effect upon capillary pressure, because of the marked resistance to blood flow in the arterioles. A constriction of arterioles raises arterial pressure and lowers capillary pressure and venous pressure, whereas a dilatation of arterioles allows the blood to flow rapidly and forcibly into the capillaries—the arterial blood pressure falls, but capillary and venous pressure rise. Venous pressure changes affect capillary pressure directly and almost quantitatively, in marked contrast to the minimal influence of arterial pressure upon capillary pressure. By injecting hypertonic or hypotonic solutions into the blood stream the direction of fluid exchange across the capillary wall may be varied at will. The forces thus involved are far greater than those acting in the normal, delicate balance between plasma proteins and capillary hydrostatic pressure.

THE CONDITIONS IN THE CENTRAL NERVOUS SYSTEM

The dural sac (for we cannot consider intracranial pressure unrelated to intraspinal pressure) is not a rigid box, but it approaches one. The elasticity of the spinal dura, and in infants of the fontanelles, is well known—but the best proof that the circulation through the central nervous system may not be correctly considered similar to that through rigid tubes (as would be the case if the dural sac were a rigid box) is furnished by the direct observations in cats by Forbes and Wolff (17) that with the skull intact and intracranial pressure within physiological limits, the flow in the meningeal veins is steady, not pulsatile. Were the central nervous system rigidly enclosed, for every cubic centimeter of blood driven into the cranium simultaneously with each heart beat, an equal quantity would have to be driven out, by way of the veins, for no increase in total volume within the rigid box would be possible. The flow throughout the system would be pulsatile. This condition is truly approximated within the eye where the flow in capillaries and veins is normally pulsatile throughout—the sclera is nearly indistensible.

This distinction between a wholly rigid container and one that is partly rigid is important. The cranium is rigid, except in infants, but the spinal dural sac is definitely distensible, and the two communicate freely with one another. In the horizontal position the spinal and intracranial pressures are equal, perhaps 100 to 150 mm. of water. When the upright position is assumed the spinal pressure increases and the intracranial pressure decreases, so that in the vertical position there is actually a negative pressure within the cranium (in an infant the fontanelle becomes depressed) which may be estimated at about 150 to 300 mm. of water, whereas the lumbar pressure has increased to about 300 mm. of water. Even the pressure in the cisterna magna is negative in the vertical position, and the zero point, where atmospheric pressure equals cerebrospinal fluid pressure, is perhaps 50 mm. below this point. Were the cerebrospinal fluid confined in a truly rigid container, at a positive pressure of 150 mm. of water, a negative pressure in the cranium could not occur on assuming the upright position. These pressure relationships are interestingly discussed by Pappenheim (18).

If fluid exchange in the cerebrospinal fluid spaces is truly analogous to fluid exchange across capillary wall in general, it follows that intracranial pressure can only be modified by factors which modify the spinal fluid pressure directly (*i.e.*, volume changes within the cerebrospinal fluid spaces), the capillary pressure within the cranium, or the relative osmotic pressure of the blood and cerebrospinal fluid. The effect of osmotic pressure variations of the blood have been already touched upon and will not need repetition here.

RELATIONS OF INTRACRANIAL PRESSURE AND ARTERIAL PRESSURE

The relations of intracranial pressure to arterial pressure are too complex to be discussed completely in so short a review. Fortunately, however, one clinically important aspect of these relations—namely, the effect of changes of intracranial pressure upon arterial pressure—has been so adequately studied that it can be summarized at the outset in a few words. On the other hand, the possible effects which primary changes of arterial pressure may have upon intracranial pressure are only vaguely—and in the main incorrectly—described; and it is chiefly to a discussion of these aspects of the problem that this section of our paper will be devoted.

a. The effects of variations in intracranial pressure

1. The study of the effects of increasing intracranial pressure upon general arterial pressure came to its full expression in the classical

work of Cushing (19); and this, in turn, received its only fundamental amplification in the often overlooked report of Eyster, Burrows and Essick in 1908 (20). From the work of these investigators it is possible to draw the following conclusions:

(a) Increases in intracranial pressure to levels lower than the mean or diastolic pressure in the extracranial artery measured have no effect upon the pressure in that artery.

(b) With increases greater than this, however, arterial pressure rises steadily, maintaining a general level just above the level of intracranial pressure, but subject, under certain conditions, to wave-like fluctuations just above and below the intracranial level.

(c) The mechanism of this rise in general arterial pressure is a reflex systemic vaso-constriction, occurring chiefly in the splanchnic area and in the limbs, which takes place only when the central vasomotor organization is intact.

2. In contrast to these definite effects from *increases* of intracranial pressure, the experimental *reduction* of intracranial pressure is without consistent alterations in the level of arterial pressure. This has been demonstrated repeatedly in the work of all of those who have studied the pressure responses to the intravenous injection of hypertonic solutions, Weed (21), Weed and Hughson (22), Foley and Putnam (23), Sachs and Malone (24). This fact is of great importance, and has been insufficiently stressed. It will be considered further at a later stage in our discussion. The observations of Block and Oppenheimer (25) and of Bailliart, Magniel and Saragea (26) that a fall of arterial pressure occurs when cerebrospinal fluid is drained, are not supported by sufficient data to be entirely dependable, and are entirely without the necessary check of simultaneous observations on the changes in venous pressure. Such a fall in arterial pressure, however, would be expected when intracranial pressure is lowered, on theoretical grounds, from the fact that raising or lowering intracranial pressure raises or lowers the resistance to blood flow through cerebral veins and capillaries, and hence throughout the cerebral vascular bed.

The fact that intracranial pressure may be increased up to at least the diastolic pressure without changes in general arterial pressure due to vasomotor response, is a most important point. It is seen commonly in patients with brain tumor in whom the intracranial pressure may be over 500 mm. of water without appreciable rise in systemic arterial pressure. The explanation is that although the general arterial pressure has not risen, with every rise in intracranial there must be a corresponding rise in *intracranial arterial pressure* due to the

fact that increasing the resistance to blood flow through a vascular bed will raise the pressure in the vessels feeding that bed. It has been shown recently that tying the femoral vein at once raises the blood pressure in the femoral artery. Similarly increasing the resistance to blood flow through the head, which is just what a rise in intracranial pressure does, is bound to raise the arterial pressure within the head. This is undoubtedly the explanation for the observation of Bailliart (26) of high blood pressures in the retinal arteries (which receive their blood from within the cranium) in the presence of increased intracranial pressure, even when the systemic blood pressure is within normal limits.

This mechanical rise in intracranial vascular pressure with rising intracranial pressure can be visualized as follows: Normally there is a steep pressure gradient as the blood flows through the head from the arterial entering pressure of the internal carotids at perhaps 1100 mm. of water to the venous exit at a pressure of about 100 mm. of water or less. As the intracranial pressure is raised, the cerebral venous pressure is also raised, but the entering pressure (*i.e.*, general arterial pressure) is unchanged, hence as the venous intracranial pressure and cerebral pressure become higher the pressure gradient becomes flatter, until the cerebral venous pressure nearly equals the entering pressure at the internal carotids. If these pressures became equal there would be no gradient—no flow would occur and the vessels would collapse with the next rise in intracranial pressure. Before this occurs, however, the vasomotor center suffers from anemia and the general arterial pressure is raised by splanchnic vaso-constriction. Thus with every rise in intracranial pressure there will be a rise in the pressure of all the vessels within the head, most marked in the veins and capillaries, and least marked in the largest arteries—quite independent of any vasomotor response in general arterial pressure.

In fact, raising intracranial pressure, by increasing the total resistance to blood flow in the body, should theoretically raise the general blood pressure much as vaso-constriction in a portion of the vascular bed would do, and the rise in general blood pressure which Cushing described must be aided to some extent by this factor. Conversely, lowering the intracranial pressure must decrease the resistance to blood flow through the cranium and must decrease the pressure in all the intracranial vessels to some extent. By decreasing thus the total resistance to blood flow in the body, decreasing intracranial pressure should theoretically tend to lower the general blood pressure, as men-

tioned above. When hypertonic solutions injected intravascularly are the means of lowering the intracranial pressure this effect might be entirely masked by the increase in blood volume. The pure effect would best be seen when cerebrospinal fluid is withdrawn.

b. The rôle of arterial pressure in intracranial pressure

With this brief summary of the effects which changes in the level of intracranial pressure produce in the level of arterial pressure, let us turn to a consideration of the rôle of arterial pressure in determining the level of intracranial pressure. Here it is necessary to make a distinction between the slow, indirect effects which arterial pressure changes may have through altering the conditions of fluid elaboration (and these are slight), and on the other hand, the *immediate, direct, mechanical* results of alterations in arterial pressure. It is with the latter question alone that this discussion will be concerned.

From the literature of this subject, one received the impression that blood pressure is often thought of as exerting an actual physical pressure upon the tissues around the blood vessel. The extent to which this is true of venous blood pressure will be discussed in the section of this paper which deals with that problem; but an attempt will be made here to prove that such a view of the situation is wholly erroneous for arterial blood pressure. It is partly from this fallacious picture of arterial blood pressure compressing the brain that the idea that arterial pressure has a direct effect upon intracranial pressure has gained currency. Becht (27), for example (p. 123, paragraph 11), uses this hypothetical direct effect to explain the fact that cerebrospinal fluid pressure can be higher than venous pressure—a fact for which it is possible to find sounder reasons.

This idea, that arterial blood pressure represents a direct pressure of intravascular blood upon other contents of the cranium, has been strengthened by the great difficulty which everyone has experienced in demonstrating the presence of active vasomotor reflexes in the intracranial vessels. This has led to a tendency to underestimate the independent contractile power of these blood vessels (Hill (13), p. 75). And yet it seems to us that from three sources evidence is already available to show that within the head, as throughout the body, the contractility of the arterial wall is a controlling factor in blood pressure relationships.

(a) The pulse pressure, for instance, within the Circle of Willis is at least 25 mm. Hg. (20); yet the pulsatile variations in intracranial pressure is only 2 to 4 mm. of water—a condition which obviously

could not exist if the brain itself were giving active support to the vessel walls of the arterial tree. Even with the intracranial pressure experimentally raised to the level of diastolic pressure, converting the head practically into an Erlanger sphygmomanometer around the intracranial arteries, the maximal pulsations which are thus produced remain negligible in size, compared to the intravascular pulse pressure change during the cardiac cycle, as can be seen in Becher's recent studies with the Franck capsule (28).

(b) Further proof of the powerful independent contractility of the intracranial vessels is seen in the fact that high degrees of negative pressure can be produced within the head without altering arterial pressure (21), (22), (23), (24). In the first place, it would be impossible to produce a negative intracranial pressure at all, if the intracranial arteries did not possess a powerful contractile tone: for in the absence of such arterial tone, every effort to reduce intracranial pressure would be accompanied by a corresponding increase in the volume of intracranial blood, and as the effort was pushed further, the animal would gradually bleed into his cranial vessels—in the same sense in which it is said that an animal in shock bleeds into its splanchnic vessels. Also, the negative intracranial pressure in upright position would be accompanied by marked dilatation of the cerebral arteries. In the second place, the absence of marked pressure readjustments in the general arterial circulation is evidence that the intracranial arterial tonus is strong enough and responsive enough to compensate for the often sudden withdrawal of any external support, and for the marked increase in the volume of circulating blood which these injections of hypertonic solutions produce. One is forced to conclude, therefore, that "Hirn-druck" is not a force which lends active support to the walls of arteries and arterioles down almost to the capillaries; that is, on the familiar blood pressure curve, it is not until beyond the high arterial pressure plateau, close to the capillary bed and beyond, that intracranial pressure becomes a factor of moment in sustaining the vessel walls balancing in part the intravascular pressure.

(c) Finally, there is a growing body of direct evidence from microscopic observation of the behavior of living pial vessels that, at any rate, the blood channels on the surface of the brain possess powerful and responsive contractility (Florey (29), Jacobi and Magnus (30), Forbes and Wolff (31)).

It must be concluded, therefore, that the intracranial vessels possess a powerful contractile tone, which must respond with local myotatic stretch reflexes, as do all muscular tissues, to chemical influences and

to vasomotor reflex influences as well. This means that a change in arterial pressure may be met almost immediately by an increased tension of the intracranial arterial walls, with almost no resulting change in the volume of intracranial arterial blood; under these conditions, no immediate change in intracranial pressure can occur, unless through arteriole dilatation the arterial pressure rise were transmitted directly to the capillary bed.

It is necessary to keep this clearly in mind in analyzing the efforts which have been made to demonstrate a direct effect of changes in arterial pressure upon the level of intracranial pressure.

Investigations such as those of Enders (32), Block and Oppenheimer (25), in which no attention has been paid to the accompanying changes in venous pressure are obviously inconclusive. Lee (33) shows that small doses of histamine can produce a simultaneous fall in arterial and intracranial pressures, with a rise in systemic venous pressure; but in this part of his work he did not register intracranial venous pressure. Hill ((13), p. 48) claims that, with a constant venous pressure, intracranial pressure will follow arterial pressure, but he fails to give any adequate evidence to support this. The most important actual experiment is that of Becht (27), pp. 67-71. He allowed the venous blood to overflow from a short, upright manometer in the torcular Herophilii, after administering adrenaline intravenously. Under these conditions, in five dogs, he could demonstrate almost as great a change in intracranial pressure as occurred when the venous blood was not allowed to overflow. He feels justified in concluding, therefore, that the rise in intracranial pressure is due to the change in arterial pressure, and not to the great general rise in systemic and intracranial venous pressures which follow the administration of adrenaline. It is clear, however, particularly in the dog, with its abundant emissary venous pathways from the head (Eyster, Burrows and Essick (20)), that a general rise in intracranial venous pressure cannot be prevented by allowing the venous blood to overflow at low pressure from one of these pathways alone.

Indeed, it is from Becht himself (27) that some of the strongest evidence can be gathered to prove that arterial pressure has little direct effect upon intracranial pressure. Assembling the data which he gives (pp. 34-38) from several experiments upon dogs, in which he observed the spontaneous changes in pressures over several hours, one finds that:

1. Arterial pressure and cerebrospinal fluid pressure changes in same direction 39 times. Arterial pressure and cerebrospinal fluid pressure changed in opposite directions 15 times. One changed and one remained unchanged 4 times.

2. Arterial pressure and venous pressure changed in same direction 38 times. Arterial pressure and venous pressure changed in opposite directions 16 times. One changed; other unchanged 4 times.

3. Thus, in 38 out of 39 times, arterial and cerebrospinal fluid pressures moved in the same direction; venous pressure also moved in that direction. On the 15 other occasions in which arterial and venous pressures did not move together, intracranial pressure followed venous pressure and not arterial pressure.

4. Finally, six occasions can be found in which the venous pressure changed less than 3 mm. (saline), while arterial pressure and intracranial pressure changed significantly. On three of these occasions, arterial and intracranial pressures moved in the same direction, and on three occasions they moved in opposite directions. . . . In contrast to this, out of 56 separate readings, venous pressure and intracranial pressures moved in the same direction 50 times.

No more striking demonstration is needed of the close correlation between venous and intracranial pressures, and of the almost complete freedom of intracranial pressure from direct and immediate influence from variations of arterial pressure.

THE RELATION OF VENOUS PRESSURE TO INTRACRANIAL PRESSURE

The effect of varying intracranial pressure upon intracranial venous pressure will be only touched upon here. Weed (11) has shown that venous pressure follows intracranial pressure changes within certain limits, and that particularly when the intracranial pressure falls well below the atmospheric pressure the venous pressure fails to follow.

The effect of raising the intracranial venous pressure is well known, both experimentally, *i.e.*, in tying the jugular veins, and clinically in sinus thrombosis. Whether intracranial venous pressure be raised by local obstruction or by a rise in general venous pressure, the effect is the same—the intracranial pressure follows venous pressure changes almost quantitatively, and this is what would be expected from what has already been said about the intimate relation of capillary pressure to venous pressure, and fluid exchange. There is one other factor here which works in the same direction, that is, the volume increase in the cerebral veins due to rise in venous pressure, for a certain elasticity of the dural sinuses exists, and perhaps more in the cerebral veins. The degree to which the venous cerebral blood volume may be increased by increased venous pressure will depend upon whether the veins were already distended or partially collapsed before the venous pressure rise takes place. In jugular compression,

as practiced clinically, the sudden marked rise in intracranial pressure is undoubtedly due more to cerebral venous and capillary congestion and volume increase than to increased cerebrospinal fluid formation, as is suggested by the fact that on jugular compression release the spinal fluid pressure falls promptly to the initial level.

THE EFFECT OF BRAIN TUMORS ON CEREBROSPINAL FLUID

Brain tumors may raise intracranial pressure either by obstructing the cerebrospinal fluid pathways so that less fluid is absorbed than is formed, or by compressing the vein of Galen or other cerebral veins, thus raising the capillary pressure in the choroid plexus and increasing the rate of formation of fluid. The actual volume increase due to the tumor is a factor of less importance, because this is in part compensated by cerebral atrophy. The mechanism of the vicious circle by which a tumor obstructing the cerebrospinal fluid pathways produces a progressively rising intracranial pressure and a progressive internal hydrocephalus, has already been described by one of us in detail (F.-S. (1)).

The easiest way to understand the relative influences of arterial and venous pressures upon intracranial pressure is by watching the excursions of the column of cerebrospinal fluid in a stand-pipe manometer at lumbar puncture.

Here we see the cerebrospinal fluid pressure responding to the variations in arterial blood pressure due to each cardiac contraction. This arterial pressure variation is about 500 mm. of water in the larger arteries, and must be nearly this value in the internal carotid as it enters the cranium. In the circle of Willis the pulse pressure is at least 340 mm. of water, yet the response in intracranial pressure is a rise of only 2 to 4 mm. of water with each heart beat. At the same time we may observe a respiratory oscillation in the manometer, which is a response of intracranial pressure to variations in intra-thoracic pressure transmitted chiefly via the jugular veins to the cranium. The variation in intra-thoracic pressure in normal respiration is not over 60 mm. of water, and the variation in jugular venous pressure due to it must be somewhat less, yet the cerebrospinal fluid pressure varies 5 to 10 mm. of water in response to it, with each respiration. No more clear-cut evidence is necessary of the relative independence of cerebrospinal fluid and arterial pressure, and the marked dependence of cerebrospinal fluid pressure upon venous pressure (provided osmotic pressures are constant).

GENERAL SUMMARY

The cerebrospinal fluid, filtered from arterial blood in the capillaries of the choroid plexus into the ventricles, and reabsorbed from the subarachnoid space into the venous blood of the dural sinuses, is but a special example of the intercellular fluids of the body. The volume and pressure of the cerebrospinal fluid are maintained by a delicately balanced osmotic and hydrostatic equilibrium between the cerebrospinal fluid and the arterial and venous blood.

A general discussion is offered of the chief factors influencing fluid exchange in such an equilibrium, namely the character of the membrane, osmotic pressure and hydrostatic pressure. Finally the special conditions of intracranial pressure are studied in the light of these fundamental considerations of fluid exchange.

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CHAPTER VIII

SOME EXPERIMENTS ON INTRACRANIAL PRESSURE IN MAN DURING SLEEP AND UNDER CERTAIN OTHER CONDITIONS

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MOSSO, in 1881, wrote a treatise on "The Circulation of the Blood in the Brain of Man." In this book he attempts to show that sleep is associated with a decrease in the intracranial pressure which he thought was due to a cerebral anaemia. His work is based on experiments on three patients and the tracings illustrating his theory seem to cover too short a period to be convincing. His apparatus resembled our own, but was somewhat more complicated and not so sensitive for, obviously, it did not always record falls in the intracranial pressure (see p. 137, fig. 53).

Since Mosso's time the anaemic theory of sleep has been a popular one with physiologists. This theory has been supported by such workers as Tarchanoff, Villemin, Leonard Hill, and Prof. Wm. H. Howell of Johns Hopkins. On the other hand, there have been workers who have taken the view that sleep was caused by cerebral congestion; amongst these are Kennedy (1877), Langlit, Regard, Czerny, and Shepard. There are other, perhaps less popular, theories or at least partial explanations of sleep among which may be mentioned the neuronc theory of Cajal and Duval. The number of these theories and the prevalence of the anaemic theory of sleep seem to depend on the lack of direct observation or experiment upon the brain itself during sleep. Howell, for example, assumes that, since the blood vessels of the extremities are dilated during sleep (as he has shown by plethysmographic experiments), the blood vessels of the brain must be relatively empty.

Some years ago, on the service of Dr. Foster Kennedy at Bellevue, we had the opportunity of making direct observations on two cases of brain hernia during sleep. During the past year, on the same service, we have studied two more cases. In a fifth case we have

studied Jacksonian epilepsy in a patient with a brain hernia. In two of these cases we have made observations on the intracranial pressure under various other conditions. These two cases had a subtemporal decompression with a cerebral hernia over which the dura had been cut and left unsutured.

Our apparatus was simple and is illustrated in figures 43 and 44. We are demonstrating here nineteen tracings taken during sleep; thirteen were made during natural sleep and six while the patients were under the influence of hypnotics. These all show that the in-

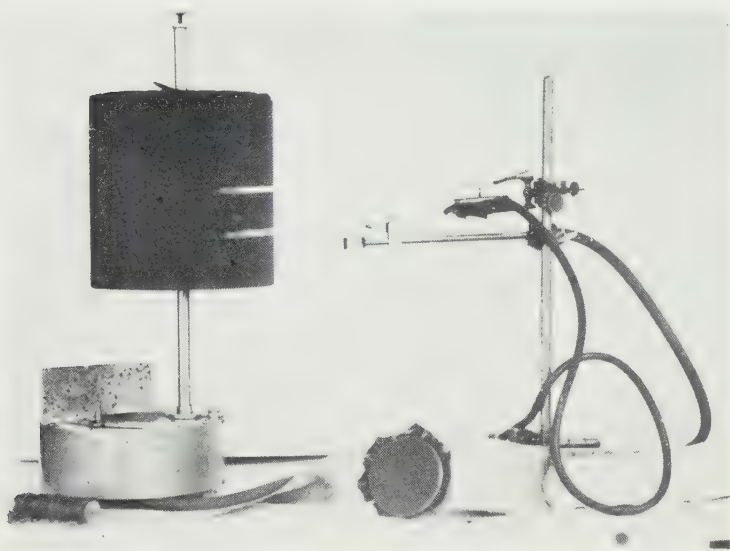


FIG. 43

tracranial pressure rises as the patient falls asleep—this increase of pressure being maintained during sleep—and falls again to its normal level when the patient awakes. In our cases the process of falling asleep was a gradual one, the intracranial pressure rising slowly for a matter of ten minutes before the patient was sound asleep and before the curve reached its highest level. On the other hand, awakening is effected in a shorter time and is accompanied by a more sudden change of the pressure.

In some of the tracings obtained under ideal conditions, where the

patient was aroused and again fell asleep, we have found a rhythmic fluctuation in the upward tendency of the curve as the patient falls asleep. We feel that this has some significance in the theory of sleep which we espouse.

Two of us have made observations on the fundus during sleep while the patients were under the influence of paraldehyde, the pupils having previously been dilated with homatropin. No change of color of the fundus or in size of the retinal vessels could be seen as compared with their appearance while awake.

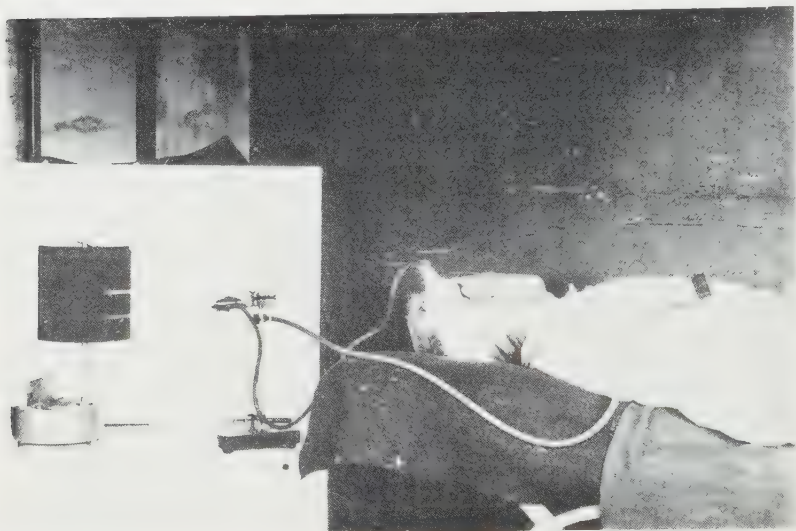


FIG. 44

The plethysmograph tracings of the arm made by Professor Howell and illustrating his "Text-book of Physiology" (p. 266) have a remarkable resemblance to our tracings obtained from the brain during sleep. We believe that the change in volume shown in these two series of tracings is attributable to the same phenomenon, namely, increase and decrease of blood volume.

During sound sleep the respirometer shows the thoracic breathing to be much deeper than when the patient is awake.

Figures 43 and 44 illustrate the apparatus.

Figure 45 shows three tracings made during sleep (Pappas) and

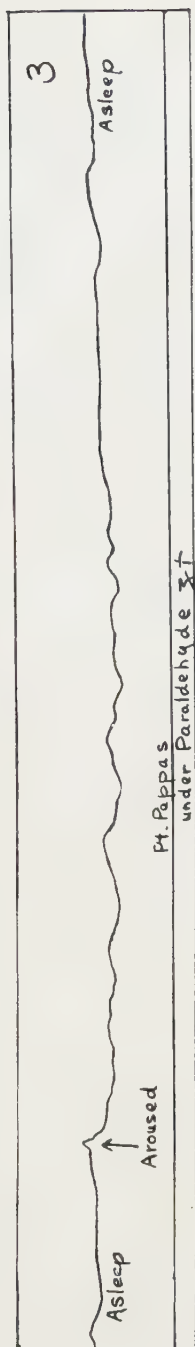
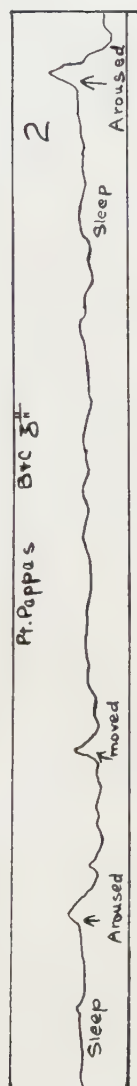
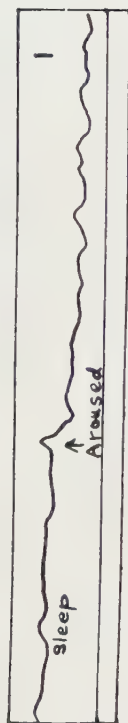


FIG. 45

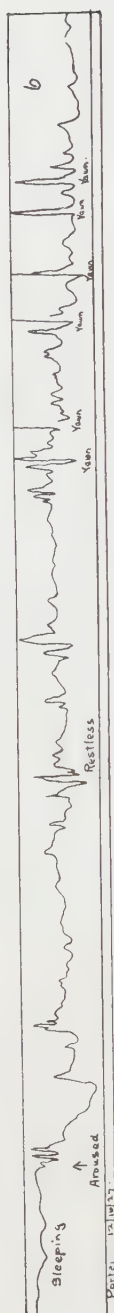
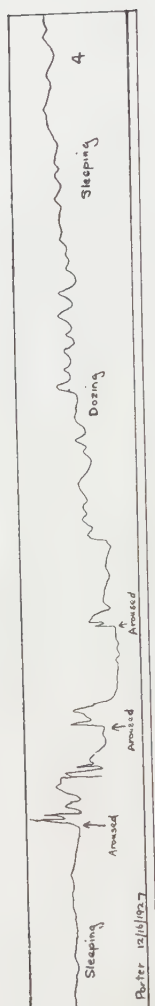


FIG. 46

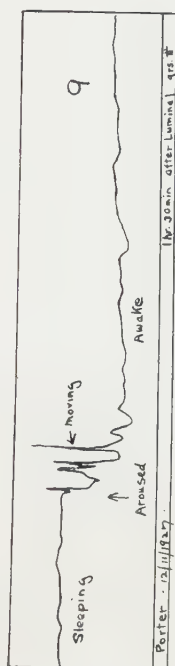
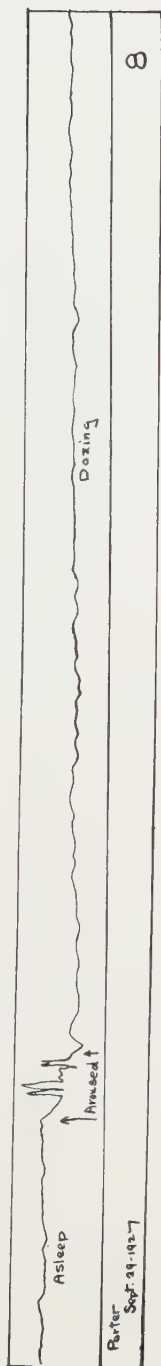


FIG. 47

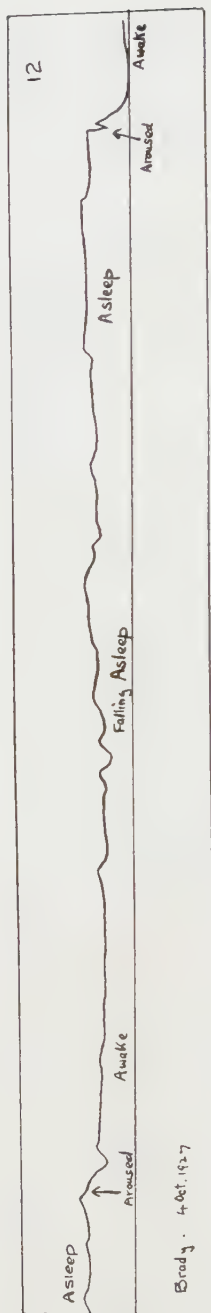
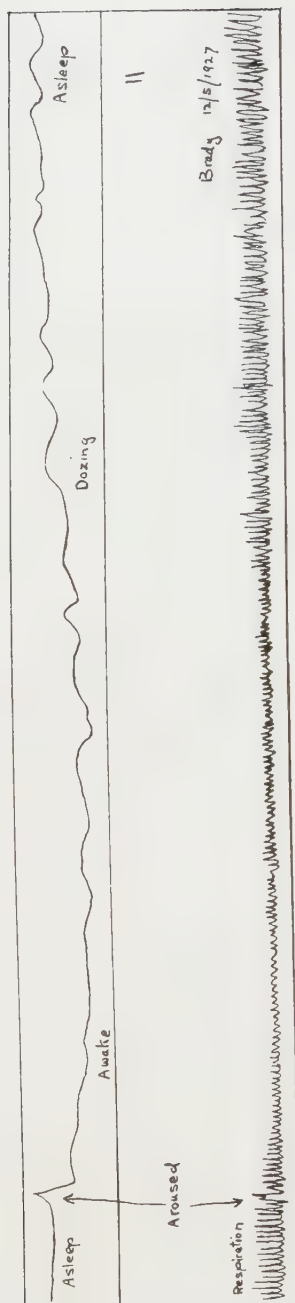


FIG. 48

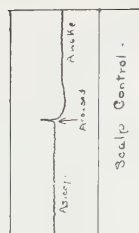
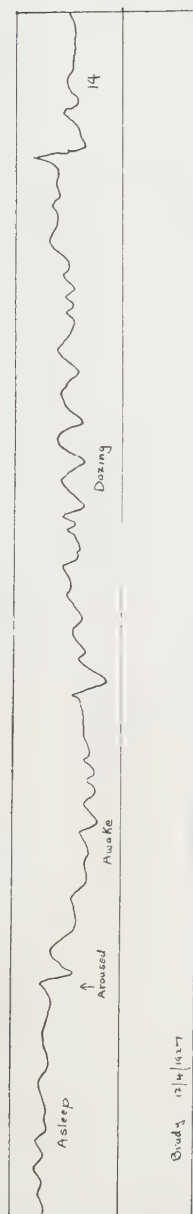


FIG. 49

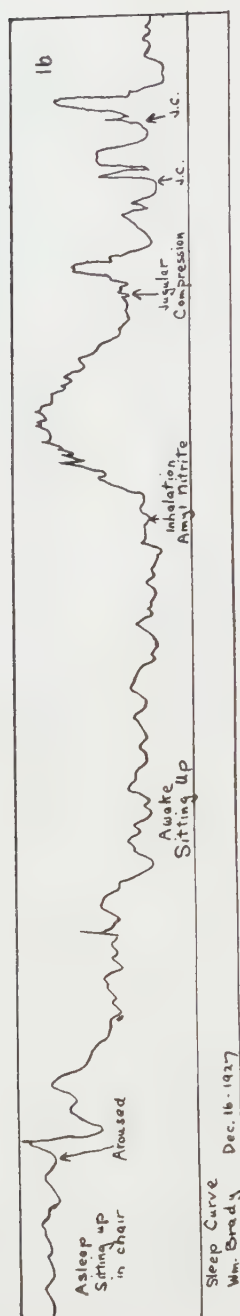


FIG. 50

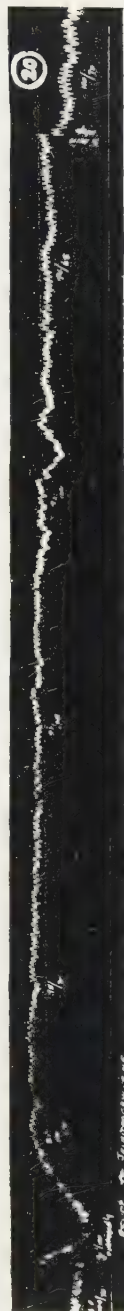
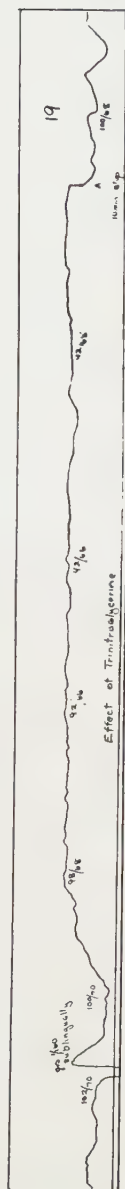
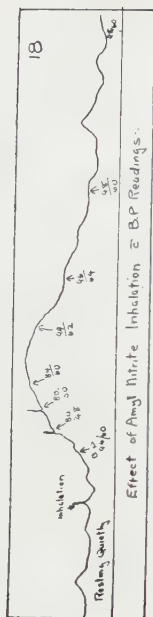
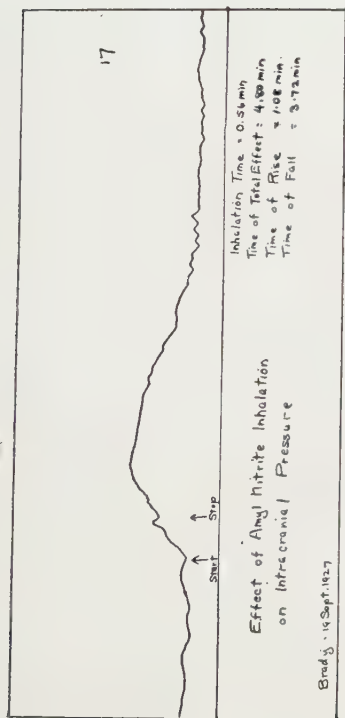


Fig. 51

when the patient was aroused. Tracing 3 in this figure shows that our apparatus was not registering properly a fall in the intracranial pressure, as can be seen from the very slight pulsation in the lower part of the curve.

Figure 46 shows three more sleep curves (Porter). Tracings 4 and 5 show an initial rise due to sound stimuli while attempting to awaken the patient. When he is fully aroused the level is seen to fall. Curve 6 shows a series of yawns which reduce the pressure.

Figure 47 shows three more sleep curves (Porter).

Figure 48 shows three more sleep curves (Brady).

Figure 49 shows three more sleep curves (Brady) and these show dozing with gradual, rhythmic rise of pressure until the patient is finally asleep.

Figure 50 shows a sleep curve (Brady) while the patient was sitting in a chair. After he was aroused fully, he was given an inhalation of 5 minims of amyl nitrite. Later jugular compression was applied for periods of ten seconds. Note here that the fall in pressure is much greater than in the tracings taken when the patient was lying down.

Curves 17 and 18 of figure 51 show a marked sudden rise of intracranial pressure during the inhalation of 5 minims of amyl nitrite and for about one minute after the inhalation is stopped. The pressure then fell rather rapidly. During the rise in the curve the blood pressure dropped from 94 systolic, 50 diastolic to 80 systolic, 48 diastolic. By the time the intracranial pressure had returned to normal, the blood pressure was normal. Curve 18a is a scalp control showing the pulsation of the left temporal artery although the strap of the tambour was still over the hernia. Curves 19 and 20 show the effect of a solution of glonoin given in doses of $\frac{1}{100}$ and $\frac{1}{100}$ of a grain sublingually. These curves show rather a rapid rise of pressure after ninety seconds. This rise was maintained for about twenty minutes. The blood pressure in each case fell from 104 systolic, 70 diastolic to 92 systolic, 66 diastolic.

Curve 21 of figure 52 was made on a case of Jacksonian epilepsy with almost continuous fits. Gas, oxygen, ether anesthesia was induced and maintained for one hour. The fits stopped in about two minutes and did not recur until the patient awoke about five hours later. At the end of thirty minutes of anaesthesia, the intracranial pressure reached its maximum, this level being maintained for the rest of the hour, and it was the same as the level at the peak of the

fits. When the anaesthetic was stopped, the pressure fell considerably, but was still not quite normal at the end of forty-five minutes. The blood pressure fell from 136 systolic, 80 diastolic to 122 systolic, 80 diastolic during the anaesthesia. Curve No. 22 shows that chloroform kept the intracranial pressure at a level equal to that during the peak of the fit. Chloroform was given about thirty minutes, and five minutes after it was stopped the patient began to have fits again, although the intracranial pressure had not fallen appreciably. Ether anaesthesia was then started and the fits stopped, but the pressure in the head fell considerably. Ether was given for thirty minutes. After the ether was stopped the pressure again fell and the fits recurred one hour later.

Curves 23 and 24 of figure 53 show the effect of morphine given subcutaneously in doses of $\frac{1}{4}$ grain. Five minutes after the injection, the pressure began to rise gradually, reaching its maximum at the end of twenty minutes. The effect lasted about eighty minutes. There was no change in blood pressure. Since morphine increases the intracranial pressure, it would be safer not to administer it for the relief of headache in brain tumor. Curve 25 shows the effect of hyoscine given subcutaneously in a dose of 150 grain. The pressure showed a rise similar to that of morphine but not quite so marked. There was no change in blood pressure.

In curves 27, of figure 54, 12 minims of pituitrin (Squibb's surgical and obstetrical) given hypodermically showed a slight, gradual fall, followed by a delayed, slow rise. In curve 28, 9 minims were given very slowly by vein over a period of five minutes. This caused a gradual rise of pressure after ten minutes. During the last part of the injection the blood pressure rose from 102 systolic, 66 diastolic to 116 systolic, 78 diastolic. In curve 29, 10 minims were given intravenously and this caused an immediate, marked rise of pressure, followed within a minute by a gradual fall, together with an increase of blood pressure from 106 systolic, 70 diastolic to 130 systolic, 76 diastolic. At the end of 4 minutes the intracranial pressure was normal; the patient vomited and had a bowel movement.

Curve 30, of figure 55, shows the effect of $2\frac{1}{2}$ grains of caffeine sodio-benzoate intravenously. The pressure began to fall at the end of one minute and reached its minimum at the end of three minutes. The effect gradually wore off, lasting about twenty-seven minutes altogether. Curve 31 shows the effect of 5 grains intravenously.

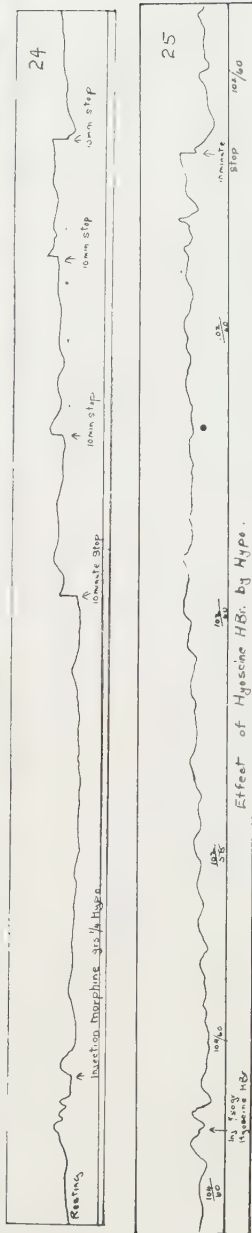


FIG. 53

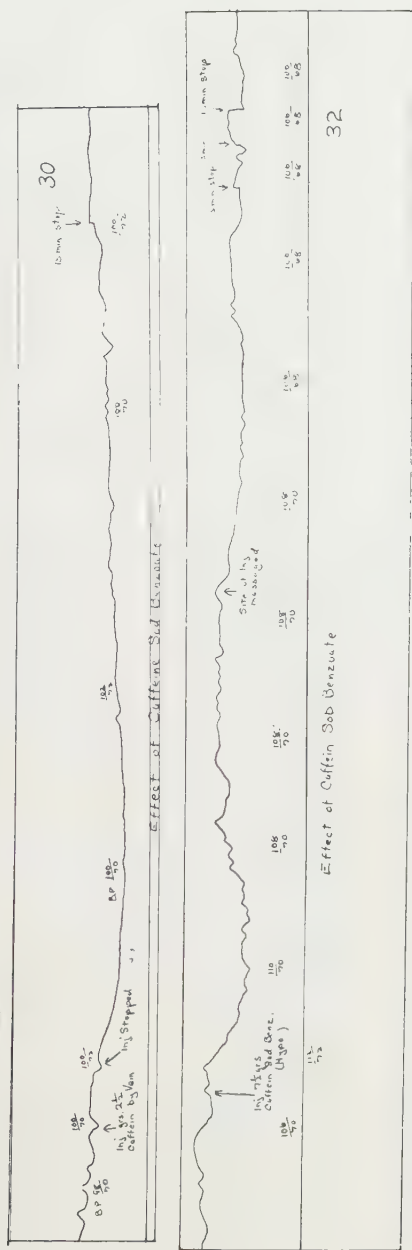




FIG. 56

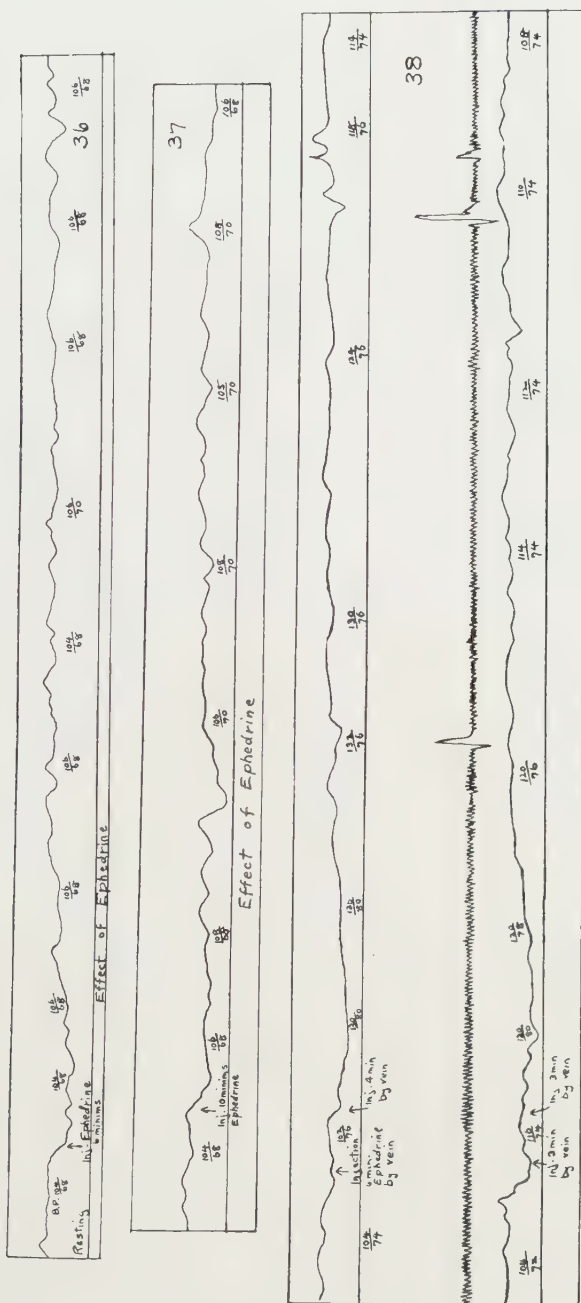


FIG. 57

There was an immediate fall with its greatest effect at the end of three minutes and lasting about twenty-five minutes altogether. Curve 32 shows the effect of $7\frac{1}{2}$ grains subcutaneously; there was a similar fall which was repeated when the site of injection was massaged. The effect of the drug was still present at the end of forty minutes. Respirometer tracings taken along with this curve showed some increase in respiratory rate. In none of these experiments with caffeine was there any change of blood pressure.

Curves 33 and 34 of figure 56 show the effect of 2 ounces of whiskey by mouth; curve 35, 1 ounce by mouth.

Curves 36 and 37 in figure 57 show the effect of 6 and 10 minims of ephedrine sulphate subcutaneously (equivalent to $\frac{1}{4}$ and $\frac{1}{2}$ grain). There is a slight immediate fall lasting about three minutes, but no change in blood pressure. Curve 38 shows the effect of the same dosage intravenously; the tracings are similar but the blood pressure rose slowly from 104 systolic, 74 diastolic to 120 systolic, 80 diastolic with 6 minims, and to 136 systolic, 80 diastolic with 10 minims. This increase of blood pressure lasted about twenty minutes.

Curve 39 figure 58 shows the effect of 12 minims of adrenalin (solution 1 to 1000) given subcutaneously. Here there is a gradual rise, reaching its maximum in nine minutes and lasting about seventy minutes. There was no change in blood pressure. Curve 42 shows the effect of 2 and 3 minims by vein. There was an immediate fall in pressure, together with a rise in blood pressure and an increase in amplitude and force of the hernial pulsation. These conditions lasted about three minutes and were followed by normal blood pressure and pulsation, but there was a delayed increase of intracranial pressure lasting more than twenty minutes. Curve 41 shows the effect of 4 minims by vein. There was an immediate rise in intracranial and blood pressure, closely followed by an increase of amplitude and force in the hernial pulsation. These conditions lasted five minutes and were followed by a normal blood pressure and hernial pulse and a delayed rise of intracranial pressure, which was still at its maximum at the end of 15 minutes. With 2 minims intravenously, the blood pressure was increased from 100 systolic, 64 diastolic to 124 systolic, 70 diastolic; with 3 minims to 156 systolic, 74 diastolic; with 4 minims to 190 systolic, 110 diastolic. Curve No. 42a is a scalp control. We feel that the immediate rise in curve No. 41 in place of the fall seen in the other curves is due to the great rise in blood pressure which overcomes the vaso-constriction of the cerebral vessels.

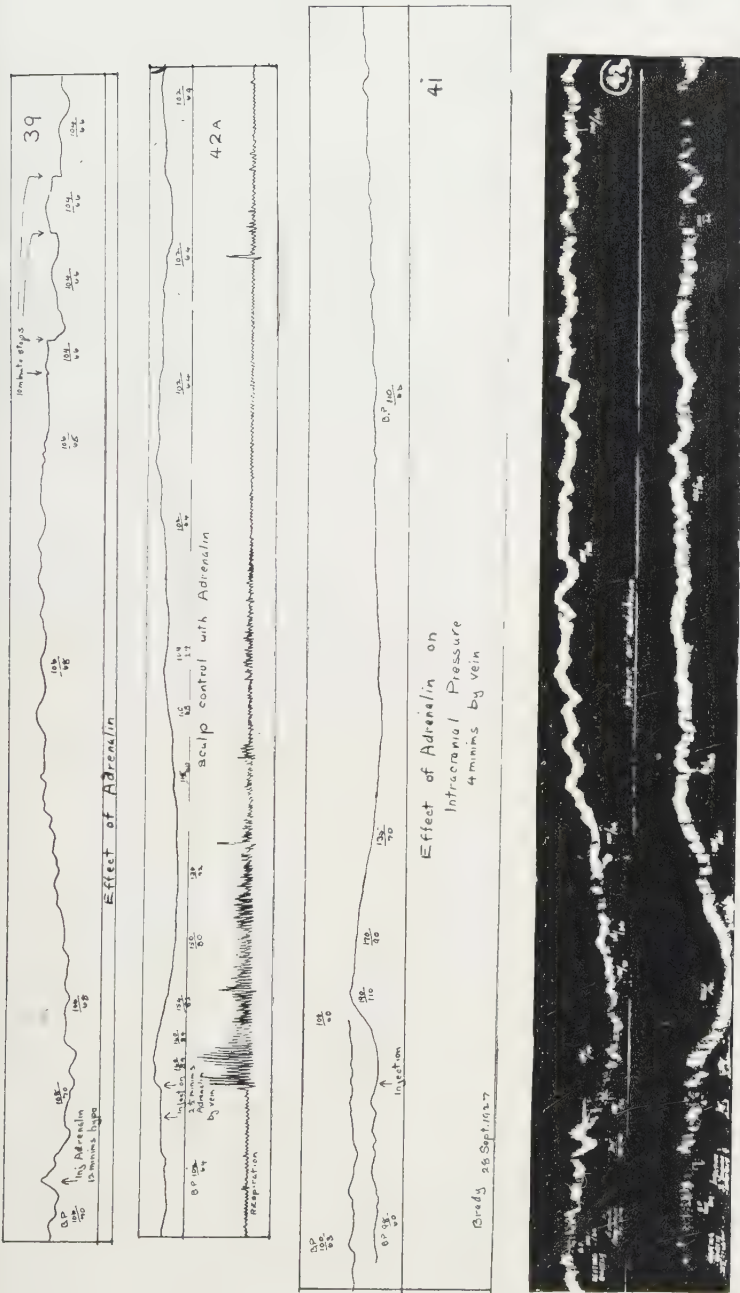


FIG. 58

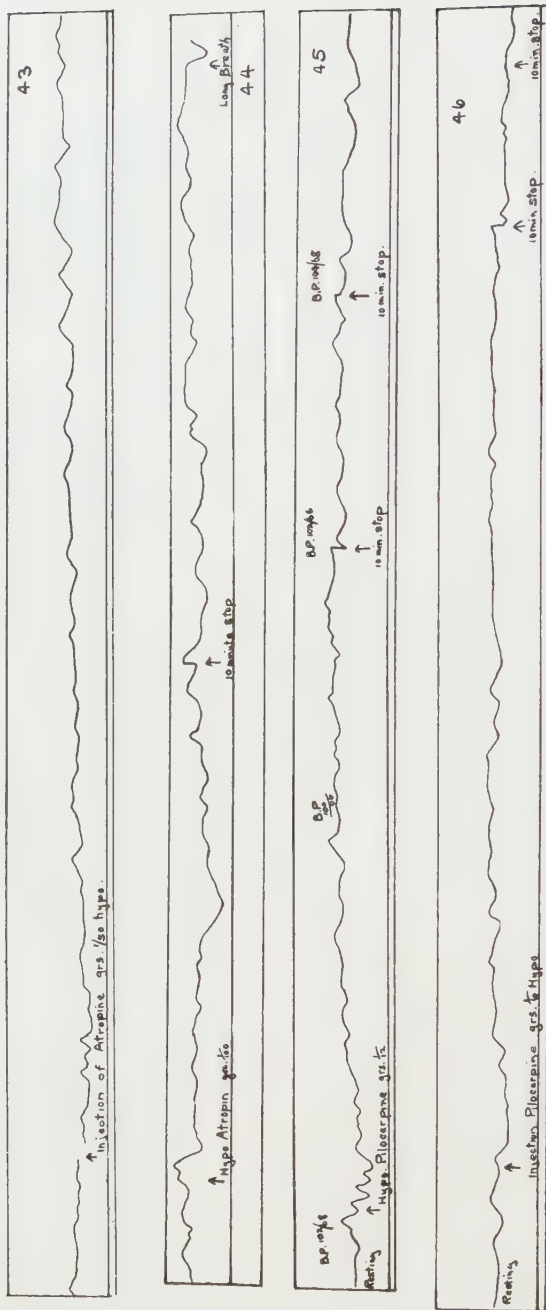


FIG. 59

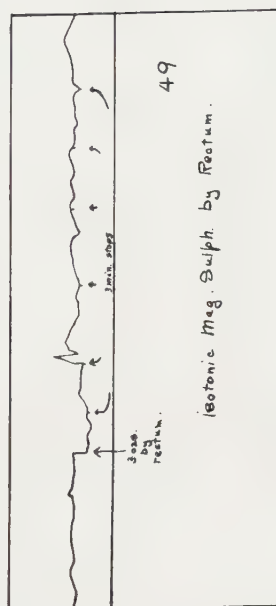
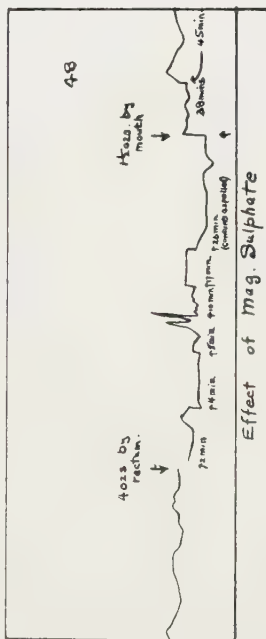
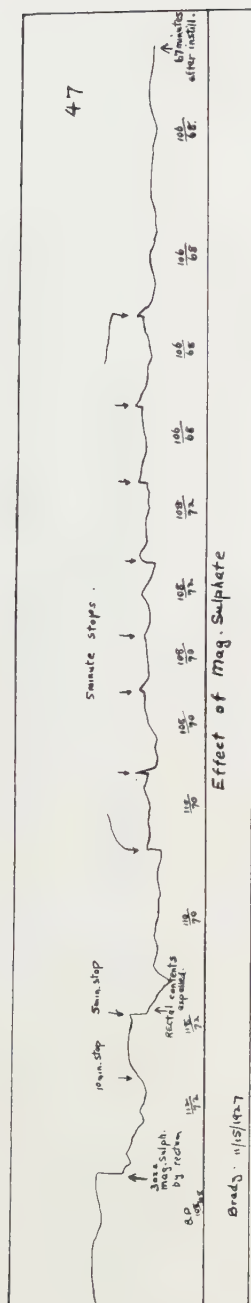


FIG. 60

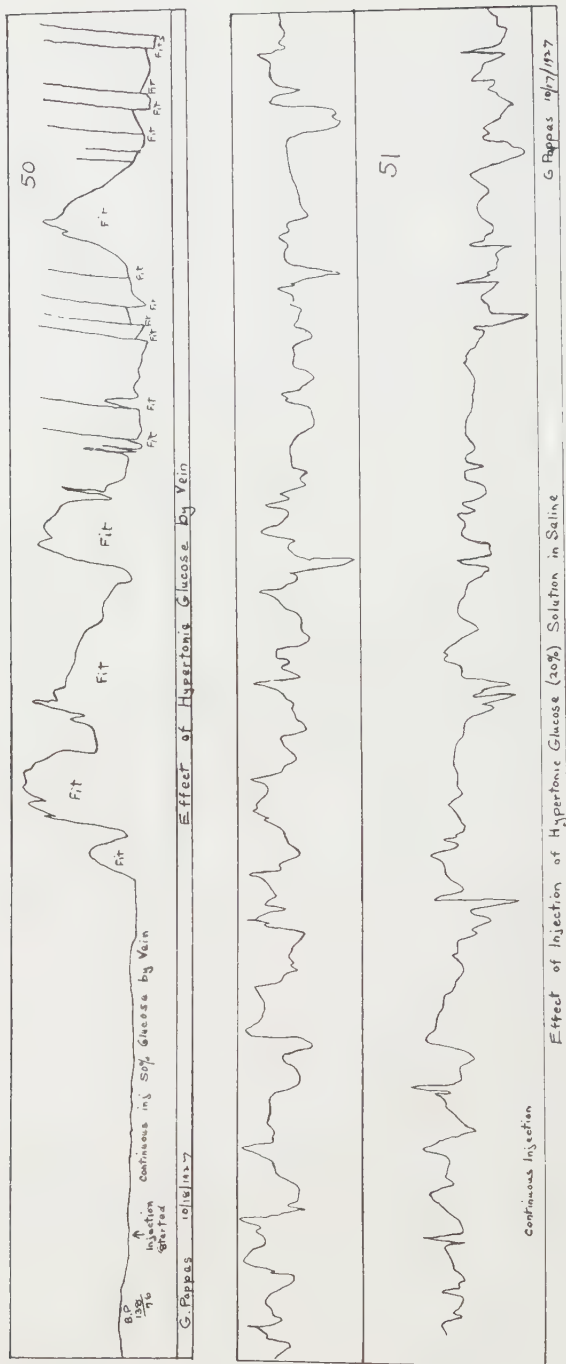


FIG. 61

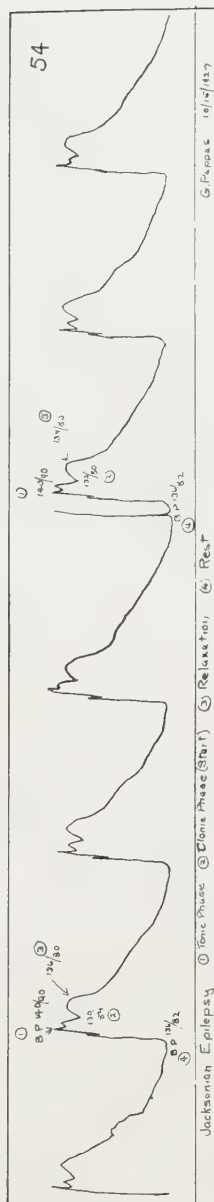
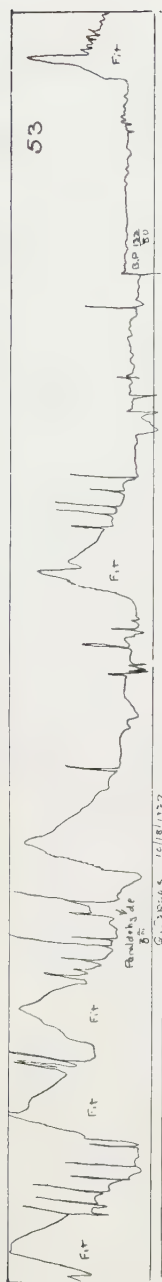
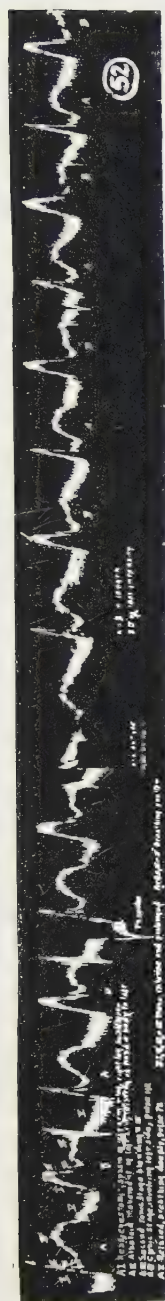


FIG. 62

Curves 43 and 44 of figure 59 show no change of pressure following the administration of atropin subcutaneously in doses of $\frac{1}{100}$ and $\frac{1}{50}$ grain. Curves 45 and 46 show a slight, gradual rise following the subcutaneous injection of pilocarpin in doses of $\frac{1}{12}$ and $\frac{1}{6}$ grain.

Curves 47 and 48 of figure 60 show the effect of 4 ounces of saturated solution of magnesium sulphate by rectum. There was a fall in pressure at the end of twelve minutes, although the enema was not fully retained. Curve 49 shows the effect of isotonic magnesium sulphate by rectum; no change.

Curve 50 of figure 61 shows a moderate, gradual fall in pressure following the intravenous injection of 40 cc. of 50 per cent glucose solution (ampoule). This injection initiated a series of convulsions in our patient with Jacksonian epilepsy. Curve 51 shows the effect of 100 cc. of 20 per cent glucose (ampoule diluted with normal saline); a similar decrease of pressure was noted and the fits became more frequent and severe.

Curve 52 of figure 62 shows that 20 minims of paraldehyde intravenously had no definite effect in our case of Jacksonian epilepsy. Curve 53 shows the effect of 3 drachms of paraldehyde by mouth; the period between convulsions was prolonged and their severity decreased. Sleep was induced twenty minutes after the end of the tracing. Curve 54, Jacksonian epilepsy with blood pressure readings during the different stages of the fit.

Curves 55 and 60 of figure 63 show the effect of deep breathing with pneumograph tracings below. Curve 56 shows the difference in intracranial pressure between lying down, sitting up, lying down and standing up, with the added effect of deep breathing while standing. Curve 57 shows the relative effect of amyl nitrite, straining, and jugular compression with pneumograph tracing with the patient sitting up throughout the experiment.

Curve 58 of figure 64 shows calibration. The apparatus was applied and a tracing made with the patient (Brady) at rest lying down. The tube was then cut and connected with a mercury manometer (Baumanometer). The air pressure was again re-established within the apparatus so that the pointer reached the original level; this pressure was found to be 12 mm. of mercury. Amyl nitrite was then given (5 minims by inhalation) and caused a rise equivalent to 6 mm. of mercury. A cough caused a rise equal to 5 mm. of mercury. Deep breathing (6 deep breaths) caused a fall of 3 mm. of mercury.

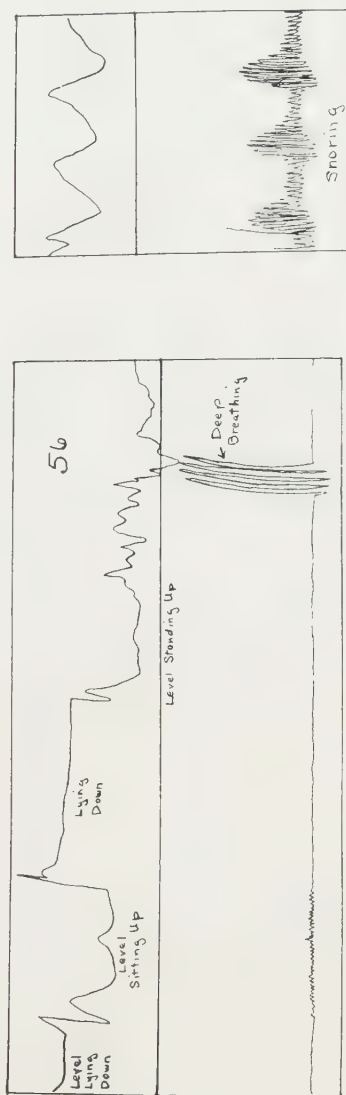
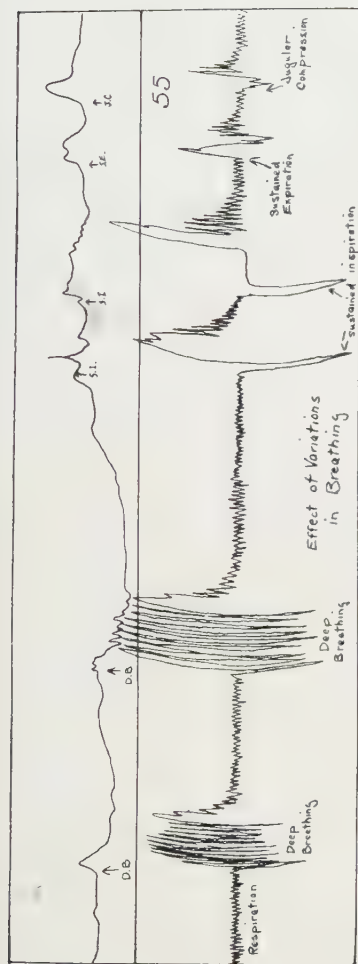


Fig. 63

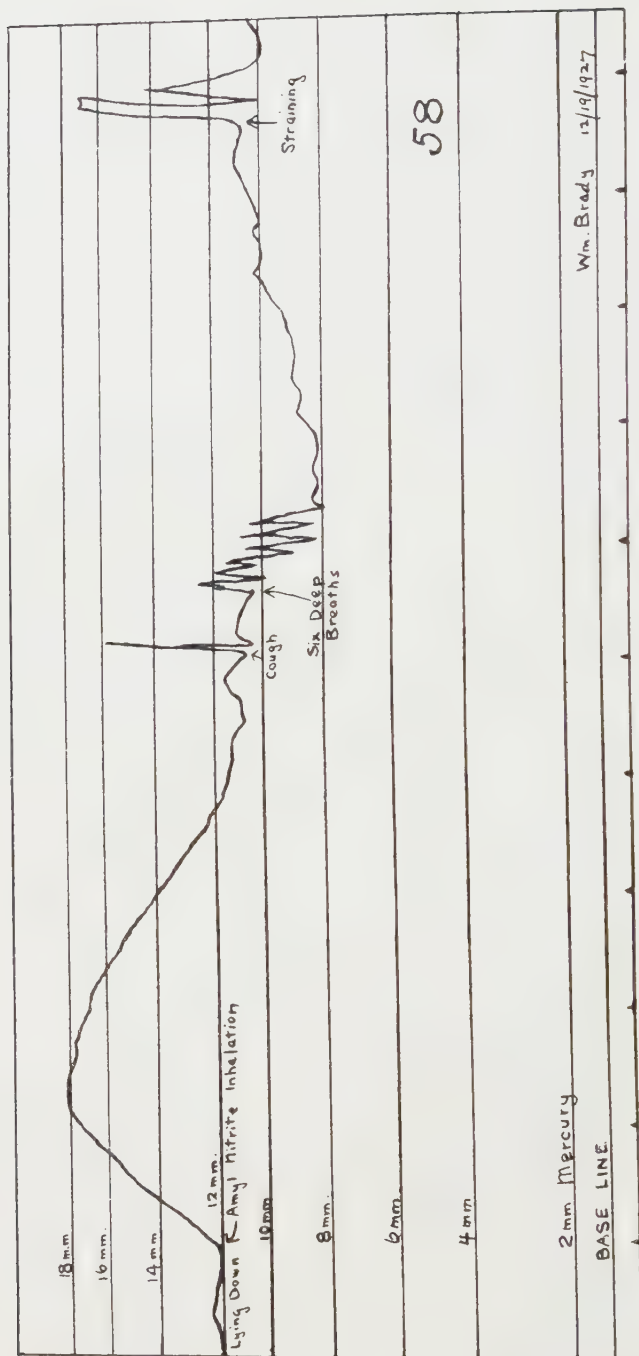


FIG. 64

Straining caused a rise of 6 mm. and a secondary rise of 3 mm. of mercury. Each ruled division represents 2 mm. of mercury. A sleep curve, according to this calibration, would mean that the intracranial pressure is raised from about 2 to 6 mm. of mercury, depending on whether the patient is lying down or sitting up when he falls asleep. The difference of pressure in the head between the sitting up position and lying down is about 4 mm. of mercury.

Some other tracings were made following the administration of luminal, bromide and chloral by mouth, but these showed no effect on the intracranial pressure within an hour.

A few observations were made with the spinal manometer. The basic spinal fluid pressure with the patient lying down was 150 mm. of spinal fluid. Five minims of amyl nitrite caused a rise to 285 mm. Two minims of adrenalin by vein caused a slow rise to 205 mm.; the blood pressure rose from 105 systolic to 165 systolic. Deep jugular compression for ten seconds caused a rise to 350 mm. With the patient sitting up and his head erect, the pressure rose to 470 mm. Caffeine sodio-benzoate intravenously ($2\frac{1}{2}$ grains) caused a fall to 120 mm.

In another patient, 3 grains of caffeine sodio-benzoate by vein caused a fall from 155 mm. to 119 mm.

Following these observations, caffeine has been used during brain operations at Bellevue in order to reduce the intracranial tension before opening the dura. Caffeine sodio-benzoate was given intravenously in doses of 6 grains for this purpose.

This principle may also explain why caffeine relieves headache due brain tumors.

CONCLUSIONS

1. The intracranial pressure is increased during sleep. The pressure gradually rises until the patient is sound asleep, when the curve reaches its maximum, and this is maintained at a fairly constant level during sound sleep. On awakening, the pressure falls rather rapidly again to normal.

2. There is an increase of the intracranial pressure on lying down.

3. Partial sleep or drowsy states are associated with a rhythmic increase of the intracranial pressure, which is not so high as during sound sleep.

4. Certain drugs which are known to affect the nervous system as

sedatives or as stimulants depend in part for their effect upon a hitherto unappreciated mechanical factor, namely, an increase or a decrease of the intracranial pressure. Morphine, for example, is a sedative which causes an increase of the intracranial pressure, while caffeine, a stimulant, produces a fall.

5. The intracranial pressure is, within wide limits, independent of the blood pressure.

6. Our conception of the physiology of sleep, arrived at from a study of our experiments and those of other workers, is as follows: We believe that the sympathetic center in the brain which maintains vasomotor tone in the vessels becomes periodically fatigued. This results

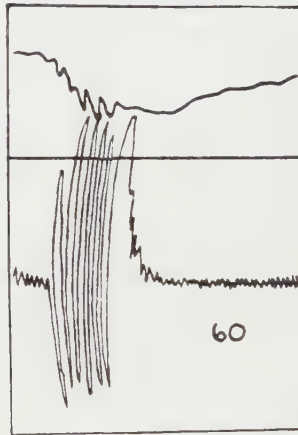


FIG. 65

in a vaso-dilatation of the blood vessels of the brain as well as those of the periphery. Accompanying this, as further evidence of fatigue in the sympathetic system during sleep, are the constricted pupils, the slower heart rate, and the decrease of blood pressure.

This vaso-dilatation in the brain would result in one of two things:

(a) The brain volume would be increased with a consequent pulling apart of the neurons (diaschisis). This might result in a physiological interruption of function in the manner suggested by Cajal and Duval when they assumed that the dendrites of the nerve cell were contractile.

(b) The cerebrospinal fluid would be increased in pressure within

the brain and especially in the pericellular spaces, thus altering the conductivity of the synapse.

Figure 65 is a diagram to illustrate the mechanical effect of dilatation of cerebral vessels.

DISCUSSION

The following questions submitted to Dr. Stevenson before the Commission, together with the answers to them, are here reported verbatim.

DR. IRVING PARDEE: Does Dr. Stevenson consider a rise in intracranial pressure the cause of sleep or is it merely an accompaniment of it? How does he correlate the absence of sleep in many conditions of increased intracranial pressure?

DR. LEWIS STEVENSON: All we can say at present is that it is an accompaniment of sleep, although we have suggested the manner in which it might cause sleep. The pressure is not very much increased. As far as we can measure it in millimeters of mercury, it is between 4 and 6 mm. of mercury, that is, where we are dealing with patients whose pressure is already increased. It may be, more in the normal subject. In other states of increased intracranial pressure, other factors enter, such as pain, which may defer sleep. That is, pain stimuli coming into the vaso-constrictor, sympathetic center, would naturally cause a temporary fall of pressure.

DR. H. G. WOLFF: What happens to the venous pressure during sleep?

DR. STEVENSON: It is said by other workers that the venous pressure falls during sleep. We have made no observations ourselves on the venous pressure.

DR. W. PENFIELD: Can you rule out the effect of partial obstruction to respiration which occurs during sleep? Could the rise of intracranial pressure be secondary to a disturbance of the intrathoracic venous pressure caused by respiratory change as in snoring?

DR. STEVENSON: We have found that deep breathing or snoring decreases the pressure within the head; at the same time during sleep where the breathing is deeper we have shown that the intracranial pressure is also greater.

DR. SPILLER: Do you know of any evidence supporting the idea of a contraction of the dendritic process? Do you think that the pressure, which you have stated is very marked, could be sufficiently great to break the synapse and separate the different neurons from one another? Do you believe that the pressure is sufficiently great to affect the nerve cells so as to destroy their function during this period of sleep?

DR. STEVENSON: Attempts have been made to demonstrate contractility in the dendrites and they have all been unsuccessful. We have suggested that instead of contractility in the dendrites, they might be slightly moved apart by a total increase in the bulk of the brain, due to this enormous increase in the vascular content of the brain during sleep. Whether that happens, we have no direct evidence. Whether this slight pressure we note is sufficient, we are not at all sure.

DR. L. S. KUBIE: Could the dilatation of the extracranial vascular bed, by tightening the bandage, produce a simulation of increase in intracranial pressure?

DR. STEVENSON: We have made several controls with the tambour on the opposite side from the hernia, for example, during the administration of amyl nitrite, where there is an engorgement of the scalp vessels. We have illustrated one of them and the rise is there but it is relatively slight compared with the rise shown in the intracranial pressure.

DR. KUBIE: Is it not possible that changes in the blood vessels in the scalp which overlies the defect in the bone may have a greater effect upon a tambour system than vascular changes in a normal area of scalp, either through the possible existence of increased vascular channels in this abnormal region, or else through a mechanical straightening out of the depressed flap as it fills with blood, and a collapse as it empties?

DR. STEVENSON: We do not think that the vessels of the scalp overlying the hernias we worked with have much to do with the increase or decrease of the pressures we have recorded.

DR. RICHARD M. BRICKNER: How do you distinguish between changes in cerebrospinal fluid pressure and in brain volume by this method?

DR. STEVENSON: We have no direct means of determining what this increased pressure is due to. We assume it is due to vascular dilatation. Our curves are very similar to Dr. Howell's curves made with his plethysmograph on the extremities where the superficial vessels are dilated. We assume that amyl nitrite causes a dilatation of the vessels, but we have no direct evidence of what the pressure is actually due to.

CHAPTER IX

AN APPARATUS TO DEMONSTRATE THE QUECKENSTEDT PHENOMENA FOR TEACHING PURPOSES

TEMPLE FAY, M.D.

SINCE the recent work of Weed and Hughson has definitely shown that the cerebrospinal fluid system can be considered as existing within a closed box, this fluid mechanism is therefore responsive to the laws of hydraulics within a closed space.

The value of the Queckenstedt phenomena, as amplified by Ayers, Tobey, Stookey and others, when properly undertaken and carefully observed, is of the highest importance. Conditions, which by their mechanical nature offer obstruction to the subarachnoid space, within the spinal canal, either directly or indirectly, or certain conditions which involve the sigmoid and lateral sinuses within the posterior fossa of the skull, can be demonstrated.

The following apparatus was devised to demonstrate the theory to the students. The apparatus consists of a glass skull, with an outlet at the base, representing the foramen magnum. Within this glass enclosed structure the content of the brain is represented by a rubber bladder filled with spongy rubber, so that it is possible to introduce into the rubber bladder, a circulation similar to the arterial venous circulation, in the human being. The arterial inflow to the rubber bladder is maintained by a direct communication; the outflow representing jugular return of blood is distinct from the arterial tube entering the bladder. Thus we have constructed, as nearly as possible, brain mass dependent upon a circulating fluid.

Outside of the bladder, and between the bladder and the glass skull, clear fluid is introduced to represent spinal fluid in the subarachnoid spaces. No communication exists between the bladder and the outside fluid. Clear fluid, between the bladder and the glass skull communicates directly with a tube connecting a piece of rubber tubing, representing the spinal canal. The spinal tubing is incased within a glass condenser filled with fluid, so as to represent the external factors of circulation and back-pressure, which may be exerted around

the dura covering the cord, by means of the peri-vertebral plexuses. The lower end of the spinal dural tubing is sealed, the length and con-

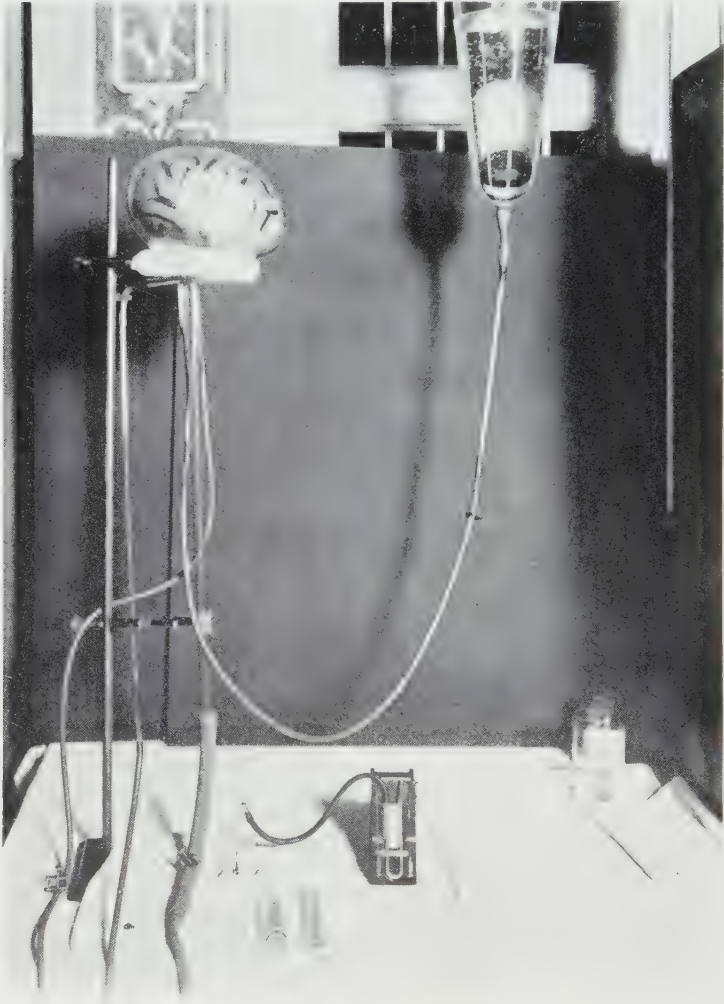


FIG. 66

sistency of the tubing being as closely analogous to dural consistency as possible. The fluid filling the spinal tubing and connecting directly

with the clear fluid outside of the bladder, between the bladder and the glass skull, represents the cerebrospinal fluid system. It is of course impossible to include the ventricles in this mechanism.

Having filled the apparatus with proper solutions and established a spinal fluid pressure of 20 in the upright position, and a circulatory pressure similar to that of a normal blood pressure, we have a sensitive mechanism which responds to mechanical stimuli.

The circulating fluid is represented by an alkaline solution of Congo red, which enters directly into the brain mass, represented within the closed bladder. Here it becomes acidified by the presence of an acid impregnating the rubber interior, and returns out of the bladder in a glass tube representing the jugular vein, with a deep blue color. The circulation is constant. The spinal pressure reading is maintained at 20. Pressure on one jugular produces only a slight rise in the mercurial manometer from 2 to 4 mm. of mercury. Pressure on both jugulars produces a prompt and definite rise to 25 and 30 mm. of mercury. Relief of pressure is followed by a prompt fall, an exact counterpart of the Queckenstedt phenomena. If now pressure be increased in the condenser fluid, surrounding the rubber tubing, representing the dural canal, reactions analogous to coughing and straining may be obtained by slight increase of the surrounding fluid pressure. This may be accomplished by a small 20 cc.-syringe connected to this closed system. The manometer immediately registers responses, rising from 20 to 40, and falling abruptly. When the neck of the spinal tube is closed between the spinal condensing system, and the subarachnoid spinal system by means of a clamp, jugular pressure produces no response in the spinal manometer, as would be expected in a complete block by the Queckenstedt. Likewise, partial block is easily demonstrated on the manometer with a slow rise and a slow fall. "Coughing and straining" responses remain normal. If the clamp be applied close to the needle, in the spinal portion of the tubing, it will be noted that neither jugular pressure, nor "coughing and straining" responses, are registered on the spinal manometer. This is in conformity with our clinical findings, and the feasibility of demonstrating spinal fluid mechanism, from the standpoint of Queckenstedt phenomena, becomes a mechanical possibility.

The student can clearly see the principles which underlie this test, and can convert them to their proper usage or variations, in his clinical experiences.

Section II

STUDIES IN DECREASED AND INCREASED INTRACRANIAL
PRESSURE

CHAPTER X

CEREBROSPINAL FLUID PRESSURE IN THE NEW-BORN

DONALD MUNRO, M.D.

THE data relative to cerebrospinal fluid pressure in the new-born presented herewith has been accumulated during the past seven years. They have been compiled from a series of 117 cases of cranial and intracranial damage. Fifty-six of these babies were discharged from the hospital dead. Of these 45 came to autopsy, the post-mortem material being subjected to both gross and microscopic examination in 23. Fifty-eight were discharged relieved. Of these 48 were followed for from less than six months to over six years. Three were duplicate entries. A detailed end result study has been presented before the Southern Surgical Association and need not be considered further at this time.

METHODS OF MEASUREMENT

Measurements of cerebrospinal fluid pressure were made by ventricular and lumbar punctures. A mercury manometer was used in every instance. The lowest figure read on the scale with the infant lying quietly on its side with the spine extended was taken as the maximum reading. The puncture was considered successful when respiratory oscillations were visible in the manometer whether or not cerebrospinal fluid was obtainable.

Six ventricular punctures were made on four cases, measurements being recorded three times. Two of these three were in a case of meningitis and can not properly be included in this study. The remaining showed an intraventricular pressure of 50 mm. This was reduced to normal by the withdrawal of 90 cc. of bloody cerebrospinal fluid. One child is now six years and one month of age and, except for a residual sixth nerve palsy, is normal in every way.

One hundred and forty-nine lumbar punctures were made on 95 cases, 139 measurements being recorded.

NORMAL PRESSURE

Sidbury (1) in 1920, has stated that the normal pressure in the newborn will probably lie between 5 and 2 mm. of mercury. On the basis of pressures recorded at discharge in babies treated for intracranial damage, and rendered symptom free by lumbar punctures, I have placed the limits as between 6 and 2 mm. of mercury.

TABLE III
METHODS OF TREATMENT OTHER THAN LUMBAR PUNCTURE

	LIVING	DEAD	TOTAL
Ventricular puncture—pressure:			
Number of cases punctured.....	2	2	4
Number of punctures made.....	2	4	6
Number of measurements taken.....	1	2	3
Highest pressure read.....	50 mm.	20 mm.	
Lowest pressure read.....		20 mm.	
Unsuccessful punctures.....	0	0	0
Pressure not recorded.....	1	2	3
Ventricular puncture—cerebrospinal fluid:			
Bloody cerebrospinal fluid {			
Greatest amount.....	90 cc.	0.25 cc.	
Smallest amount.....	2 cc.	0.25 cc.	
Number of amounts measured...	2	1	3
Purulent cerebrospinal fluid {			
Greatest amount.....		90 cc.	
Smallest amount.....		30 cc.	
Number of amounts measured...		3	3
Typical sub-temporal decompression.....	1	1	2
Elevation of depressed fracture.....	4		4
Intubation under wrong diagnosis before admission.....		1	
Intra-ventricular administration of anti-meningococcus serum.....		1	1

There were 35 such cases. In addition, 20 cases which were discharged dead came within this pressure field at their final lumbar puncture. Thus 55 showed a normal cerebrospinal fluid pressure at the final measurement before death or discharge. Sixteen cases, under the same conditions, showed a pressure of over 6 mm. of mercury. The average figure in these latter cases was about three times that of the former.

TABLE IV
NORMAL AND DECREASED INTRACRANIAL PRESSURE CHART

CLASSIFICATIONS		TOTAL	DEAD	LIVING
Decreased intracranial pressure (below 2 mm. mercury), number of cases.....		11	5	6
Normal intracranial pressure (from 6 to 2 mm. mercury inc.):				
Number of cases discharged symptom free or dead.....		55	20	35
Number of cases discharged symptom free or dead (with intracranial pressure over 6 mm.).....		16	8	8
All cases L. D. 43 28	Highest intracranial pressure on discharge.....		18 mm.	10 mm.
	Lowest intracranial pressure on discharge.....		1 mm.	2 mm.
	Average intracranial pressure.....		5.07 mm.	4.56 mm.
	Percentage dead or diseased in follow-up—all causes.....			3.57%
Cases with 6 mm. to 2 mm. pressure L. D. 35 20	Average intracranial pressure on discharge.....		3.2 mm.	3.68 mm.
	Percentage dead or diseased in follow-up—all causes.....			11.42%
Cases with over 6 mm. pressure L. D. 8 8	Average intracranial pressure on discharge.....		9.75 mm.	8.37 mm.
	Percentage dead or diseased in follow-up—all causes.....			37.5%
Disease and death percentage in follow-up	All causes	Cases with pressure of 6 mm. or under.....		11.42%
		Cases with pressure of over 6 mm.....		37.5%
	Known cerebral cause	Cases with pressure of 6 mm. or under.....		5.8%
		Cases with pressure of over 6 mm.....		25.0%

The most significant finding, however, whether considered in the light of the determinations of the normal limits of intracranial pressure or in that of the efficiency of the treatment given is in the "death and disease percentage" as revealed in the follow-up. In the cases discharged relieved but with an intracranial pressure known to be above 6 mm. this percentage was 37.5 from "all causes" and 25 from "known cerebral causes only." In those discharged with normal pressure corresponding figures were 11.4 and 5.8.

DECREASED PRESSURE

Decreased cerebrospinal fluid pressure, that is, pressure below 2 mm. of mercury and frequently present as respiratory oscillations only, occurred in 11 cases. Six of these were discharged relieved and 5 dead. In my experience this condition has only been associated with surgical shock or extreme dehydration. The number is too small to warrant the drawing of any conclusions and in any event, what figures there are should never have been available, since lumbar punctures should not be performed under such circumstances. If made through diagnostic error, however, the information obtained is of use as pointing to a grave prognosis.

INCREASED PRESSURE

In the absence of surgical shock and dehydration, increased intracranial pressure has been demonstrated at least once previous to discharge in this series in every case of depressed fracture, intracranial hemorrhage from whatever cause, cerebral oedema or cerebral congestion. However, to eliminate possible error, all original pressure measurements except those listed in table IV whether increased, decreased or normal, have been included under this heading.

It is interesting to note that the variation as between living and fatal cases, whether considered as, highest, lowest, or average pressure is insignificant. This is not in accord with figures obtained by the writer in a series of adult head injuries, (2) although from a broad point of view the pathology is analogous. In the adult cases the average pressure in the fatalities was two and one-half times higher than in the non-fatal cases. I am unable to offer a satisfactory explanation for this difference.

TABLE V
LUMBAR PUNCTURE DATA—TOTALS

	LIVING	DEAD	TOTAL
Pressure data:			
Number of cases punctured.....	56	39	95
Number of punctures made.....	99	50	149
Number of measurements taken.....	91	48	139
Highest pressure read.....	50 mm.	48 mm.	
Lowest pressure read.....	Less than 1 mm.	Less than 1 mm.	
Average pressure reading.....	10.9 mm.	11.1 mm.	
Cerebro-spinal fluid data:			
Bloody cerebro-spinal fluid, total punctures	<div> <div>Greatest amount....</div> <div>Smallest amount....</div> <div>Average amount....</div> <div>Number of amounts measured.....</div> </div>	<div> <div>19 cc.</div> <div>0.25 cc.</div> <div>4.2 cc.</div> <div>20</div> </div>	<div> <div>10 cc.</div> <div>0.333 cc.</div> <div>3.7 cc.</div> <div>22</div> </div>
<u>L.</u> <u>D.</u> 37 31			42
Clear cerebro-spinal fluid, total punctures	<div> <div>Greatest amount....</div> <div>Smallest amount....</div> <div>Average amount....</div> <div>Number of amounts measured.....</div> </div>	<div> <div>25.0 cc.</div> <div>0.25 cc.</div> <div>10.96 cc.</div> <div>7</div> </div>	<div> <div>0</div> </div>
<u>L.</u> <u>D.</u> 12 1			7
Yellow cerebro-spinal fluid, total punctures	<div> <div>Greatest amount....</div> <div>Smallest amount....</div> <div>Average amount....</div> <div>Number of amounts measured.....</div> </div>	<div> <div>17.0 cc.</div> <div>0.33 cc.</div> <div>6.9 cc.</div> <div>18</div> </div>	<div> <div>4.0 cc.</div> <div>0.5 cc.</div> <div>3.75 cc.</div> <div>6</div> </div>
<u>L.</u> <u>D.</u> 24 10			24
Contaminated bloody total Punctures	<div> <div>Greatest amount....</div> <div>Smallest amount....</div> <div>Average amount....</div> <div>Number of amounts measured.....</div> </div>	<div> <div>3.0 cc.</div> <div>0.333 cc.</div> <div>1.11 cc.</div> <div>7</div> </div>	<div> <div>1.50 cc.</div> <div>1.50 cc.</div> <div>1.50 cc.</div> <div>1</div> </div>
<u>L.</u> <u>D.</u> 16 4			8
No fluid removed, number of punctures	10	4	14
Combined cerebro-spinal fluid data:			
Greatest amount.....	25.0 cc.*	10.0 cc.†	
Smallest amount.....	0.25 cc.‡	0.333 cc.†	
Average amount.....	5.542 cc.	2.485 cc.	

L. = Living; D. = Dead.

All pressures are given in millimeters of mercury.

* Yellow.

† Bloody.

‡ Bloody or clear.

REDUCTION OF PRESSURE BY REMOVAL OF CEREBROSPINAL FLUID

In the presence of increased intracranial pressure, sufficient fluid has been removed to bring the pressure level to within the limits set as normal. This was done 135 times. The amounts were measured eighty-one times. Clear fluid was never found and measured in a fatal case. The presence of blood in the removed cerebrospinal fluid can not be considered pathognomonic of an intracranial hemorrhage, although, if followed at a later puncture by the removal of yellow fluid, it is certainly suggestive. In an average case it was necessary to remove more than twice as much fluid in the living than in the dead, before increased cerebrospinal fluid pressure could be brought to normal.

It was deemed inadvisable to remove any fluid in fourteen instances. This was chiefly because, in the earlier cases, it was considered unsafe; and ventricular drainage was instituted or subtemporal decompression was performed where the original pressure was 20 mm. or over. Later experience has shown that this precaution was unnecessary.

CONCLUSIONS

There were made 142 measurements of cerebrospinal fluid pressure on 95 new-born babies; 139 of these were made at lumbar puncture. The remaining 3 were made at ventricular puncture.

Normal cerebrospinal fluid pressure in the new-born, as determined from figures obtained from cases treated for cranial and intracranial damage and discharged symptom free, lies between 6 and 2 mm. of mercury.

Cerebrospinal fluid pressure below 2 mm. of mercury has occurred in this series only in the presence of surgical shock or dehydration.

Increased cerebrospinal fluid pressure has been present in every case of depressed fracture, intracranial hemorrhage, cerebral oedema, or cerebral congestion.

Intracranial hypertension in cranial and intracranial damage in the new-born may be safely reduced to normal by lumbar decompression regardless of the degree.

Cases discharged relieved and symptom free with a known cerebrospinal fluid pressure of between 6 and 2 mm. of mercury show a late death and disease percentage of 11.4 from all causes, and 5.8 from known cerebral causes only.

Cases discharged relieved and symptom free with a known cerebro-spinal fluid pressure of over 6 mm. of mercury show a late death and disease percentage of 37.5 from all causes and 25.0 from known cerebral causes only.

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CHAPTER XI

TRANSMISSION OF INTRACRANIAL PRESSURE IN HYDROCEPHALUS IN INFANCY

KENNETH D. BLACKFAN, M.D., BRONSON CROTHERS, M.D., AND
ROBERT N. GANZ, M.D.

MOST of the studies upon pressures within the craniovertebral cavity have been conducted upon adult human beings, or upon fully-grown animals. Obviously the adult cranium and spinal column are relatively fixed in shape and in capacity and can probably be considered as a closed box completely filled with various soft or fluid substances to which the rules of physics concerning the transmission of pressure where fluids completely fill rigid, communicating containers will apply.

We do not propose to dispute the approximate accuracy of such a conception of pressure transmission in adults, but we maintain that the rigid box idea is unsound in theory and frequently invalid in fact in the human infant.

In the first place, the skull and the spinal column of the baby are subject to expansion, contraction and distortion under everyday stresses to a degree which makes any such phrase as "closed box of constant volume" quite inapplicable. We do not have to present evidence upon this point, but merely suggest that doubters study obstetrical text-books or attend one or two obstetrical cases.

Moreover, the physical characteristics of the intracranial contents in infancy have a distinct bearing upon the question. In the first place, the central nervous system itself is softer than in the adult; secondly, the falx and the tentorium do not, as in adults, arise entirely from rigid and fixed bony insertions which cannot be distorted. In the infant the bony attachments of the tentorium are relatively fixed, but the falx arises from a suture line and is in part supported only by the elastic tissue covering the fontanelles. Clearly, the brain in so far as it is supported by the dural septa is subject to measurable dislocation when the head is distorted.

Under the various conditions which transiently raise pressure, the

cranial capacity is instantly and palpably increased by bulging of the fontanelle. Within a few days acute meningitis, or other persistent causes of increased pressure, will spread suture lines and even cause dislocation downward of the eyeballs as the orbital plates bend down.

Far from having a fixed capacity, the infant's craniovertebral cavity is thus subject to marked changes in volume, and its contents to easy movement. Under these circumstances we felt justified in reconsidering the experiments described by Leonard Hill in 1896.

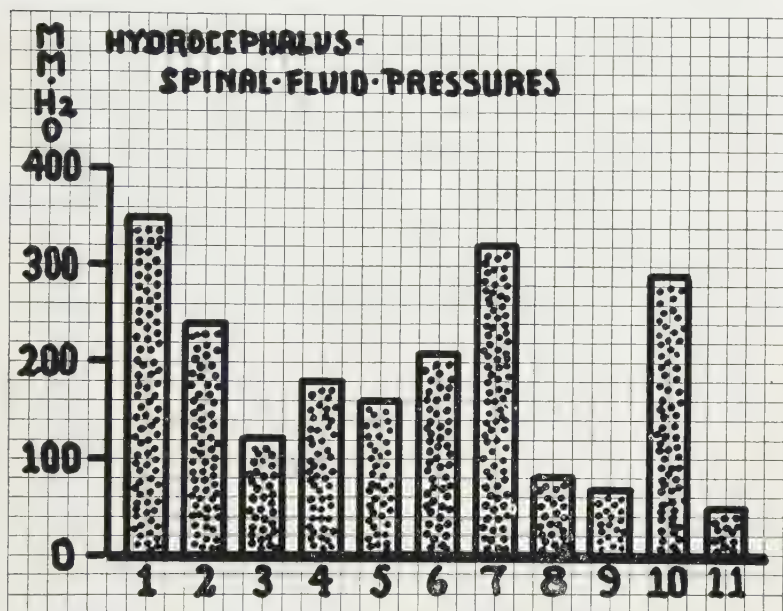


FIG. 67. Pressures in millimeters of spinal fluid in eleven successive cases

In so far as they seem valid and pertinent, Hill's conclusions were that discontinuity of pressure could be brought about at the cleft of the tentorium or at the foramen magnum. On reading his work it is obvious that by destroying the integrity of the skull he destroyed the "closed box" situation. It seems to us that his work, for the same reason that leads to valid criticism by workers with adult material, is more pertinent and interesting to pediatricians. We therefore became curious about relative pressures in infancy. We were,

at first, rather skeptically interested in isolated manometric readings of spinal pressures in infants. Our skepticism was on the whole increased by the chaotic readings we obtained.

Case 1. V. C. Age, 8 months. Hydrocephalus. Head large at birth. Increase in size noted at $1\frac{1}{2}$ months, which has continued. Pressure reading, 4-16-27, 350 mm.; 75 cc. of fluid withdrawn following tap. Thickness of skin plus cortex, $\frac{1}{4}$ inch.

Case 2. H. M. Age, 3 months. Marked hydrocephalus—sterile—developing after birth. Pressure, 120 mm. H_2O . Thickness of skin plus cortex, $\frac{1}{4}$ inch.

Case 3. J. K. Hydrocephalus from birth—sterile. Lumbar puncture performed because of full anterior fontanelle. Pressure, 240 mm. Thickness of skin plus cortex, $\frac{1}{2}$ inch.

Case 4. L. H. Age, 14 months. Hydrocephalus at birth gradually increasing. Pressure, 180 mm. Thickness of skin plus cortex, $\frac{1}{16}$ inch.

Case 5. B. J. Hydrocephalus at birth—Caesarean delivery. Pressure on third day, 160 mm.

Case 6. Syphilitic meningitis. Treated with tryparsamid only. Pressure, 210 mm.

Case 7. J. B. Age, 7 months. Sterile at time of puncture. Pressure, 320 mm.

Case 8. S. W. Age, 7 to 8 weeks. Hydrocephalus at birth. Pressure, 80 mm. Thickness of skin plus cortex, $\frac{3}{16}$ inch.

Case 9. Baby K. Age, 4 weeks. Hydrocephalus not present at birth, but gradually developing since birth. Pressure, 70 mm.

Case 10. C. P. Age, 3 months. Development of hydrocephalus after birth (between ages of 6 weeks and 3 months). Communicating type—infected. Following puncture (five days) temperature rose. Lumbar puncture revealed cloudy fluid—600—cells mostly lymphocytes—no organisms. Treated with anti-meningococci serum, with improvement. Assumption is that manipulation resulted in the breaking down of a meningococcus abscess. Pressure, 290 mm.

Case 11. Baby K. Age, 11 months. Meningococcus meningitis. Twentieth day of disease, lumbar pressure, 50 mm.

The chart shows our results. We do not for a moment expect this chart to be received with respect. With crying, restless, compressible babies, unpredictable variations seem to be inevitable. We do not believe that single manometric readings are in any way useful, or give information as to the state of the pressures within the various cavities. In particular we see no reason to suppose that spinal pressure in infants is necessarily equal to subtentorial or supratentorial pressure. We quite agree that in many cases simultaneous ocular observation of two manometers—one connected with a needle in the spinal canal, and one with a needle in the ventricle—will show ap-

parently simultaneous rise and fall of fluid. On the other hand, such apparently simultaneous variations are by no means always present.

We realize, of course, that all degrees of block in transmission of pressure have been recognized and studied under pathological conditions. More or less casually, delay in transmission has been noted. Most of these observations have been on adults.

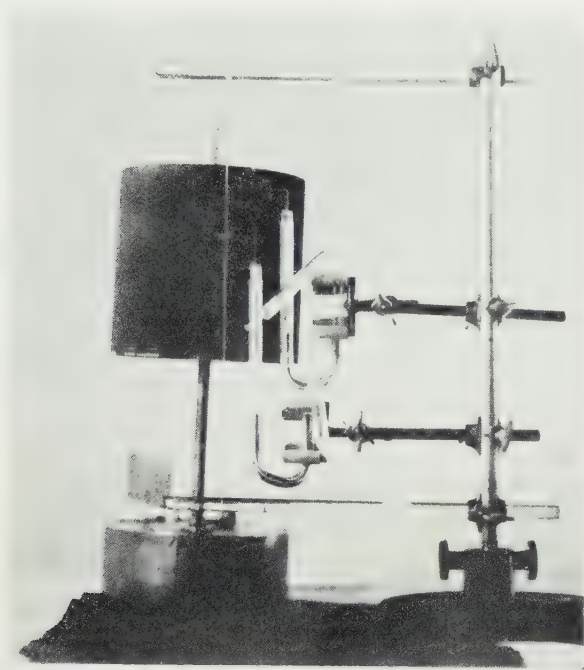


FIG. 68. Arrangement of manometers recording simultaneous ventricular and spinal pressures.

If our idea that the craniovertebral cavity of the infant is elastic and its more solid contents are loosely held in position is correct, certain definite phenomena are to be expected. If pressure is rapidly increased in the supratentorial chamber, which of course is by far the most easily expandable, it is reasonable to suppose that part of the rise will be noted only in that chamber, that it will be both delayed in time and decreased in volume as the displaced fluid flows through the narrow channels of the aqueduct and the foramina. The degree

of delay and of decrement will depend upon the size of the communicating channels.

Hydrocephalic infants furnish ideal material for such investigation. It is evident that some of them have enormously dilated channels between the ventricles and the spinal subarachnoid space, some relatively normal channels, and some none at all.

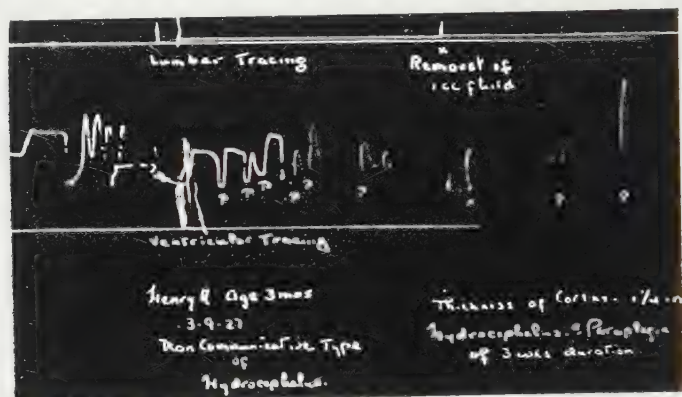


FIG. 69. Non-communicating hydrocephalus due to tumor

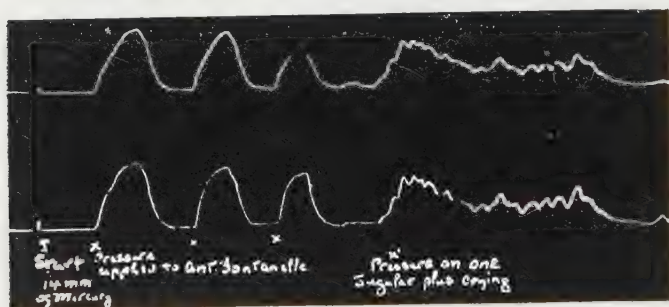


FIG. 70. Case 8. Communicating hydrocephalus with no delay or decrement. Upper tracing, ventricular; lower tracing, spinal.

Ocular observation alone is not always convincing in so far as time relations in the propagation of pressure goes. We therefore attempted to get graphic records. The apparatus is easily set up, but it is technically rather difficult, without anaesthesia, to get continuous records. Mercury manometers, connected by glass, saline filled

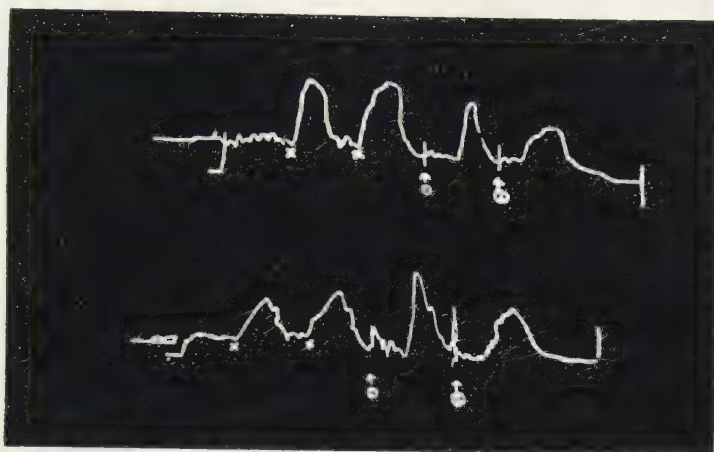


FIG. 71. Case 3. Communicating hydrocephalus with delay and decrement. Upper tracing, ventricular; lower tracing, spinal.

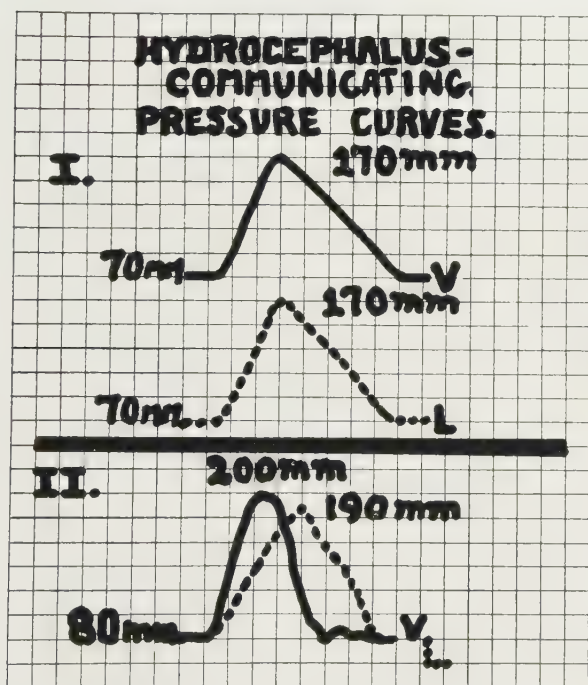


FIG. 72. I. Free communication without decrement or delay. II. Communication, but with delay and decrement.

tubing with connections of thick walled rubber tubing were used. Every effort was made to eliminate loss of fluid.

The results, although clearly lacking any authority due to numerical adequacy, seem to us suggestive.

Pressure was imposed by the simple process of compressing the vault of the infant's cranium between the hands. Academic discussion aside, this procedure vitiated the "rigid container" conception. Three types of response were seen.

1. No propagation of pressure whatever occurred. In this case tumor was responsible, as confirmed by autopsy.

2. The propagation of pressure was apparently immediate and without decrement. In this case we assumed a series of wide channels.

3. Propagation of pressure was subject to some delay and to slight decrement. Since we were particularly interested in this aspect of pressure transmission we present, in addition to the tracing which is retouched for clearness in reproduction, a curve which is corrected by accurate calibration of the entire apparatus. The curve marked *II* in figure 72 is compared to that in figure 69 which is shown as *I*.

CONCLUSIONS

In infants the contents of the craniovertebral cavity do not transmit pressure according to the laws governing the pressure relations where fluids completely fill rigid containers.

1. In hydrocephalus the propagation of abruptly applied pressure of short duration from ventricle to spinal space may be essentially immediate and without decrement. In this case we assume the probability of widened channels between the two cavities.

2. Delay in time and decrement in intensity may be noted. This suggests patent though narrow channels. Though we have no evidence upon this point, we suggest that this delay and decrement may also occur in normal infants.

3. The propagation of pressure may be completely blocked. This means, of course, that at the time of reading, at least, a complete discontinuity of pressure exists.

In general, we believe that the time element in the propagation of pressure is interesting, that it can be graphically recorded, and that it is possible that it may be made clinically useful. Certainly the reliance upon isolated measurements of spinal fluid pressure, as indicating intracranial pressures, seems to us likely to lead to serious error.

The application of the "closed box" theory to infants seems to us entirely unsound.

DISCUSSION

The following question, submitted to Dr. Crothers before the Commission, together with the answer to it, is here reported verbatim.

DR. WEED: I should like to ask Dr. Crothers if he is willing to discard entirely the Monro-Kellie doctrine in children. Several years ago Dr. Mañagas, a Filipino, showed experimentally in hydrocephalic kittens that the intravenous injection of a hypertonic solution would produce negative pressures of the intraventricular cerebrospinal fluid. Is Dr. Crothers willing to discard the whole thesis in childhood or merely to widen the limits of its relative accuracy?

DR. CROTHERS: All that Dr. Blackfan, Dr. Ganz and I wish to call attention to is that the differences in the material make a decided difference in the absolute pressures that you obtain; and also that the curve might be used as an index of the relative width of the channels in cases where obstruction is suspected. It is very evident in many cord tumors, for instance, that you can get a rise in spinal pressure upon jugular pressure, but it is a much slower rise than your intracranial rise, and we feel that the study of time relations is worth while. Physicists point out that if the walls of closed chambers are elastic the closed box theory no longer applies because all sorts of other elements enter the calculation. In these babies with wide-open sutures, and subject to distortion of the cranium, it seems quite obvious that you have, in a measure, the conditions that Leonard Hill produced experimentally, that is, translocation of brain mass as well as discontinuity of pressure from narrowing of channels. If that is true, it seems to us that it throws light not only on a possible method of study of pressure but also upon the protective mechanisms in labor because the orderly control of pressure under the obstetrical strain with the tremendous distortion of the head must depend a good deal upon mechanisms that prevent undue translocation of brain mass.

This paper merely points out that the physical conditions in infants are not identical with those in adults. We accept, tentatively and with reservations, the Monro-Kellie doctrine.

CHAPTER XII

THE RELATION BETWEEN INCREASED INTRACRANIAL PRESSURE AND INCREASED INTRASPINAL PRESSURE

CHANGES IN THE CEREBROSPINAL FLUID IN INCREASED INTRA- CRANIAL PRESSURE

JOHN S. HODGSON, M.D.

CERTAIN aspects of the relation between increased intracranial pressure and increased intraspinal pressure and the changes in the cerebrospinal fluid in increased intracranial pressure have been observed in connection with the study of 49 cases of brain lesion in which combined ventricular and lumbar puncture has been performed as an aid to localization.

The determination of the presence or absence of hydrodynamic block between ventricles and lumbar subarachnoid space and the comparison of protein values in the two loci in cases with increased intracranial and increased intraspinal pressure, forms the subject of this communication.

In 1924, in a paper presented before this Society, Dr. F. Fremont-Smith and I made a preliminary report on 22 cases of brain lesion in which combined ventricular and lumbar puncture had been performed as an aid to localization.

The number of cases so studied has been increased to 49, and our conclusions as to the value of this procedure remain essentially unchanged.

The method employed has been an adaptation of Dr. Ayer's combined cistern and lumbar puncture as used in the diagnosis of spinal subarachnoid block.

Combined ventricular and lumbar puncture may disclose the presence or absence of intracranial block, and may thereby help to localize the lesion, in a general way, as lying below or above the tentorium. The procedure also permits a complete chemical study of the cerebrospinal fluid, not only from the lumbar region, but also from the ventricles. This is important when the danger of simple

lumbar puncture in cases of papilloedema is appreciated. The temporary relief of intracranial pressure afforded by this measure is also at times essential. Information concerning the position and size of the ventricles may also be obtained.

Combined ventricular and lumbar puncture is simple and in the majority of cases may be performed under local anesthesia. We have used the posterior horn of one ventricle, generally, though, in a few cases, we have tapped the posterior horns of both lateral ventricles, and a few times have used the anterior horn.

Under normal conditions it has been shown that there is free communication between the ventricles and the spinal subarachnoid space. The cerebrospinal fluid pressures, with the patient in the horizontal plane, are equal in these regions.

Communication between ventricles and spinal subarachnoid space is, however, frequently interrupted. In such cases, we may find initial differences in cerebrospinal fluid pressure in the two loci, the lumbar being the lower. We may also find diminished pulse and respiratory oscillations, diminished response to jugular compression and release, and unequal fall in pressure upon withdrawal of fluid from either locus. This corresponds to the pressure findings in cases with spinal subarachnoid block due to cord lesions. In the absence of dynamic block pressures, oscillations, response to jugular compression and release, etc., are equal in the two loci in cases with brain lesion, as in cases of cord lesion. In cases of brain lesion as in cases of cord lesion there are, in addition to hydrodynamic, certain chemical changes, affecting largely the total protein. The protein changes in this group of cases, while suggestive, are not always specific.

We have performed combined ventricular and lumbar punctures in 49 cases of brain lesion. The diagnosis in these cases has been verified by operation or autopsy. Of these cases, 24 were subtentorial and 25 supratentorial. We have found that a certain degree of block exists in the majority of the subtentorial lesions. Among the 24 subtentorial cases 16, or two-thirds, showed block in some degree and one-third no block. Of 21 supratentorial lesions block, on the contrary, was absent in 19, slightly questionable in 1, and definitely present in only 1 of these cases, a pinealoma. Four cases of luetic meningitis are included in this group, and showed no block. The high protein values in these cases are those of an inflammatory process.

These findings correspond to those reported in 1924, except for the

greater percentage of subtentorial lesions not showing block in the recent group. Of 8 subtentorial lesions not showing block, 4 were acoustic neuromas, 1 a cerebello-pontine angle lesion, 1 a cystic dilatation of the fourth ventricle, 1 an angiosarcoma of the fourth

TABLE VI
SUBTENTORIAL

DIAGNOSIS	BLOCK	PROTEIN	
		L	V
Acoustic neuroma, right soft	Yes	267	8
Acoustic neuroma, left.....	Yes	334	10
Acoustic neuroma, left.....	No	414	66
Acoustic neuroma, right.....	No	235	51
Acoustic neuroma, left.....	No	276	380
Acoustic neurfibroma, right.....	No	400	{ R 13 L 13
Neurofibroma recess.....	Yes	26	6
Cerebello-pontine angle tumor, right.....	Yes	276	21
Fibroma left cerebello pontine angle (sarcoma ?)....	Yes	60	8
Dural endothelioma left cerebello pontine angle.....	Yes	77	9
Gliomatous cyst right cerebellar angle.....	Yes	59	11
Cyst left cerebello pontine angle.....	Yes	138	10
Arachnoid fibroma left cerebello pontine angle.....	No	181	15
Midline cyst congenital.....	Yes	66	23
Dilated cystic, fourth ventricle.....	No	19	16
Cholesteatomatous cyst, fourth ventricle.....	Yes	26	8
Glioma, floor, fourth ventricle.....	Yes	36	12
Glioma, roof, fourth ventricle.....	Yes	19	6
Glioma, floor, fourth ventricle.....	Yes	38	7
Ependymal glioma vermis and fourth ventricle.....	Yes	37	12
Angio-Sarcoma, roof fourth ventricle.....	No	62	11
Gliomatous cyst, left cerebellum.....	Yes	61	{ R 35 L 18
Gliomatous cyst, right cerebellum.....	No	24	5
Chronic meningitis (?).....	Yes	62	12

ventricle, and 1 a gliomatous cyst of a cerebellar hemisphere. The absence of block in acoustic neuromas and certain cerebello-pontine angle lesions may be explained by the possibility of local increase in size without causing pressure on the cerebrospinal fluid pathways. In the supratentorial case—that of a pinealoma, block was found.

This might be confused with a subtentorial lesion so far as this procedure alone is concerned.

The protein values in both subtentorial and supratentorial lesions are fairly suggestive. Among the subtentorial cases, two-thirds showed definite increase, and one-third no increase in protein. The 8th nerve and cerebello-pontine angle lesions, especially the former, showed an increase, at times considerable, and generally speaking, the highest in the entire group. The total protein findings in the other subtentorial cases, namely: fourth ventricle congenital abnormalities and tumors, the intracerebellar lesions and the chronic meningitis with adhesions showed protein increase in the lumbar region in 4 of 11 cases and normal protein values in the others. The ventricular protein content was generally not elevated in these cases.

The protein values in the supratentorial lesions have, as a rule, been normal in the lumbar region in the presence of normal ventricular protein. If, however, the ventricular protein is increased, as it is in 7 of 20 cases reported, the lumbar protein also shows an increase, at times being greater, but more often being less than the ventricular protein. Our explanation of high ventricular and lumbar protein is that the lesion probably lies close to the ventricular surface. This hypothesis has been confirmed by autopsy and is offered in explanation of the other high ventricular and lumbar protein values. Moreover, in a case of teratoma of the third ventricle verified by autopsy, ventricular and lumbar punctures performed on different occasions and without pressure readings showed lumbar protein of 200 and ventricular protein of 129. In the pinealoma case, which shows block, the protein was normal in the ventricle and increased in the lumbar region, in this respect resembling the findings in subtentorial lesions.

In the entire group of 49 cases in which combined ventricular and lumbar puncture has been performed the procedure has been of help in localization in all but 2 subtentorial and possibly in 2 supratentorial cases; in each of the former, there was absence of block and normal total protein. The finding, however, in the 2 subtentorial cases, of hydrocephalus enabled us nevertheless to make a correct presumptive diagnosis. In 1 of the 2 supratentorial cases there was high lumbar protein,—namely, 334, and normal left ventricular protein,—namely, 14, in the absence of block. This finding seems to be characteristic of acoustic neuromata and angle lesions, but in this case a second com-

bined puncture six days later, including both ventricles as well as the lumbar sac, showed a right ventricular protein of 308, a left of 8, and a lumbar of 348. This seems to indicate the presence of a tumor in close proximity to the surface of the right lateral ventricle.

TABLE VII
SUPRATENTORIAL

DIAGNOSIS	BLOCK	PROTEIN	
		L	V
Glioma left frontal.....	No	45	20
Glioma left frontal.....	No	40	24
Glioma right posterior frontal lobe.....	No	334	14
Cystic glioma right frontal.....	No	67	{ R 30 L 13
Cyst left fronto-temporal.....	No	55	342
Arachnoid fibroma right fronto-parietal.....	No	23	18
Varix left fronto-parietal.....	No	36	10
Glioma right temporal lobe.....	No	78	{ R 69 L 73
Glioma left temporal lobe.....	No	56	14
Glioma with softening right temporal.....	Possibly slight	114	143
Gliomatous cyst right temporal.....	No	105	
Glioma right parietal.....	No		
Glioma left parietal.....	No	27	33
Glioma right parietal.....	No	26	11
Glioma left parietal.....	No	138	103
Calcified glioma left occipital.....	No	63	100
Cystic arachnoiditis right fronto-parietal.....	No	44	28
Cystic arachnoiditis fronto-parietal.....	No	49	80
Subarachnoid cyst left temporo-parietal.....	No	44	16
Tuberculous abscess right parietal.....	No	60	82
Pinealoma.....	Yes	64	11
Teratoma third ventricle.....		200	129
Luetic meningitis.....	No	400	81
Luetic meningitis.....	No	857	285
Luetic meningitis.....	No	138	31
Luetic meningitis.....	No	40	38

The finding of block with increased lumbar and normal ventricular protein in the case of pinealoma is what we should expect, but in the absence of clinical signs suggesting a midbrain lesion it might be misleading.

There have been no deaths attributable to this procedure which therefore becomes safer than air injection as a diagnostic procedure.

SUMMARY

1. Combined ventricular and lumbar puncture has been performed in 49 instances.

2. This method makes it possible to obtain lumbar fluid in all cases, including those with high grade papilloedema with less danger of medullary injury than with lumbar puncture alone.

3. In patients with subtentorial lesions a certain degree of dynamic block between ventricles and lumbar subarachnoid space was found in two-thirds of the cases, and absence of block in one-third of the cases. This represents an increase in the latter type since our original communication in 1924.

4. In patients with supratentorial lesions block has been absent except in a case of pinealoma.

5. In subtentorial lesions the ventricular protein value is normal, while the lumbar protein value was found increased in two-thirds of the cases and within normal limits in one-third of the cases. The most characteristic increase occurs in cases of acoustic neuroma or cerebello-pontine angle lesion.

6. In the supratentorial lesions the ventricular and lumbar protein values tend to be normal except in the cases where the lesion lies close to the ventricular surface. In these instances the protein value in both loci may be increased, either one being the greater.

DISCUSSION

The following questions submitted to Dr. Hodgson before the Commission, together with the answers to them are here reported verbatim.

DR. SPILLER: Dr. Hodgson spoke of a case in which this combined method was of great value. If I understood him correctly, he said that both the ventricular fluid and the fluid obtained by lumbar puncture were yellow. The Wassermann was positive. An explanation of those findings would be desirable. Why was the yellow fluid present in the case of syphilis?

DR. HODGSON: I do not know how to explain that. We did a combined puncture expecting to find a brain tumor probably an acoustic neuroma. We were surprised when we examined the fluid to find that the Wassermann was positive and that the cells were increased. In this case I think that the puncture was of

help to us, giving us the fluid and allowing us to make the other tests which showed a luetic meningitis.

DR. SPILLER: You could exclude any evidence of block by the lumbar and the ventricular puncture?

DR. HODGSON: Yes, in that case there was no evidence of block. Some of the sub-tentorial cases that did not show a block showed a yellow fluid. I do not think that the yellow fluid necessarily means a block. I think it may be present in cases where there is no block.

DR. AYER: We have had quite a series of cases of acute syphilitic meningitis. A considerable number of these have yellow fluids,—in fact it is quite characteristic. I do not know about the ventricular fluid. We do know that dyes and serum introduced into the cisterna magna will go into the ventricle. It is reasonable therefore that xanthochronic fluid should pass from cisterna magna to ventricle.

CHAPTER XIII

ANALYSIS OF THE LUMBAR CEREBROSPINAL FLUID IN SIXTY-SEVEN CASES OF TUMORS AND CYSTS OF THE BRAIN¹

JAMES B. AYER, M.D.

THE following analysis is a statistical study of the pressure, color, protein content, cells, and goldsol reaction in a series of 67 cases.

The diagnosis was determined in all except 2 by operation or autopsy. In these 2, a pituitary tumor and a meningeoma, clinical evidence makes the diagnosis quite certain. From a study of the records the writer is satisfied that the fluid analyses were made at a time when cerebral disease was present, although in some cases considerably earlier than operation seemed warranted. Many of the cases were personally known to the writer, and uniform technique both at the puncture and in the examination of the fluid was the rule. It may be stated here that the Wassermann reaction was uniformly negative in all cases, with a single exception which on repeated examination was shown to be a mistake, and the pathology of no case suggested syphilis.

PRESSURE

It has not been the custom in our clinic to perform lumbar punctures on patients with choked discs of marked degree. For this reason in part we have adopted the method of combined ventricular-lumbar puncture to enable us to examine the cerebrospinal fluid with greater safety. As Dr. Hodgson has shown, the fluid pressure levels are nearly the same in the ventricle and lumbar sac, whether or not a partial block is present. As the combined technique calls for withdrawal of ventricular fluid before lumbar puncture is performed, the initial lumbar pressure reading is of no value, and therefore the initial ventricular value has been substituted in these cases. To this group, other cases have been added in which lumbar puncture alone has been employed.

In table VIII the initial pressure reading is presented. The read-

¹ From the Neurological Clinic, Massachusetts General Hospital.

TABLE VIII

SPINAL FLUID PRESSURE COMPARED WITH OCULAR AND X-RAY EVIDENCE OF
INCREASED INTRACRANIAL PRESSURE

	PRESSURE IN MILLI- METERS OF CEREBRO- SPINAL FLUID	FUNDI	X-RAY EVIDENCE INCREASED INTRACRANIAL PRESSURE
<i>Subtentorial</i>			
Acoustic neuroma.....	330	Atrophy	Yes
	400	Choked	No
	300	Choked	
	180	Normal	No
	250	Choked	No
Glioma.....	400	Choked	No
	600	Choked	Yes
	800	Atrophy	Yes
	400	Choked	No
	600	Choked	Yes
	350	Choked and atrophy	Yes
	150	Atrophy	No
	{ 180*	Early choking	No
	{ 360	Choked	Yes
Arachnoid fibroma.....	120	Choked	No
	220	Choked	No
	270	Choked	No
Angiosarcoma.....	500	Choked	Yes
Cholesteatomatous cyst.....	290	Choked and atrophy	
	{ 95	Normal	No
	{ 180	Normal	
	{ 210	Normal	
	{ 150	Normal	
Other cysts.....	500	Choked	Yes
	300	Choked	No
	320	Normal	No
Chronic meningitis.....	220	Normal	Yes

* Eight months later.

TABLE VIII—*Continued*

	PRESSURE IN MILLI- METERS OF CEREBRO- SPINAL FLUID	FUNDI	X-RAY EVIDENCE INCREASED INTRACRANIAL PRESSURE
<i>Supratentorial</i>			
Glioma:			
Frontal.....	600	Atrophy	?
	410	Choked and atrophy	Yes
	210		Yes
	560	Choked	No
Temporal.....	200	Choked	?
	250	Choked	Yes
	680	Choked	
	400	Choked	No
	185		
	400+	Choked	No
	120		
	200	Normal	
Parietal.....	310		
	300	Choked	
	300		
	300		
Occipital.....	140	Choked	
	425	Normal	No
	290	(?) Atrophy	No
	290	Choked	No
Meningeoma—Vertex fronto-parietal.....	480	Choked	Yes
	270	Choked	Local only
	330	Choked	No
Pituitary.....	600	Choked	
	200	Normal	No
	160	Normal (?)	Slight?
Pineal.....	550	Choked	Yes
	10		
	100	Normal	No
	50		
Metastatic carcinoma.....	250	Choked	No
Osteogenic sarcoma skull.....	270	Choked	Sarcoma only

TABLE VIII—*Concluded*

	PRESSURE IN MILLI- METERS OF CEREBRO- SPINAL FLUID	FUNDI	X-RAY EVIDENCE INCREASED INTRACRANIAL PRESSURE
<i>Supratentorial—Continued</i>			
Cholesteatomatous cyst.....	{ 185 250 175 270	Normal	No
	{ 140 430 530 150 600 200	Normal Choked Choked Choked Choked Normal	No No No Yes No
Arachnoid cyst.....	{ 120 80 210 140 180 190 85 85	Normal Normal Normal Normal Normal Normal Normal	No No No

ing is made by allowing the fluid to flow into a glass manometer of approximately 2 mm. bore. It is not claimed that the method is exact, but it has proved sufficiently reliable and accurate for clinical use.

Using this method it has been found that fluid pressures over 250 mm. are abnormally high, although it has been shown that figures above this are found in cases of vascular hypertension, uremia, etc., and do not necessarily indicate intracranial pathology. In this series, in which are listed pressures obtained in 61 patients, 42 or 69 per cent are found above 250 mm., representing a great variety of pathological processes and almost all possible intracranial loci. It would be a fascinating problem to study the height of pressure reading relative to size, position and rapidity of growth of tumor or cyst but this is not here attempted.

Perhaps the low readings are of greater importance. Pressures

below 250 mm. also occur in all groups as shown in the table, but the eye is particularly drawn to the group of arachnoid cysts, usually cortical in situation, as this group alone accounts for 6 of the 19 cases in which low pressure was found in this series.

Is estimation of spinal fluid pressure a more delicate index of intracranial pressure than the examination of the optic discs or the evidence obtained by x-ray? In the table it will be seen that fluid hypertension usually goes hand in hand with papilloedema. However, in the 19 cases showing low readings, in 6 changes were found in the eye-grounds characteristic of increased intracranial pressure. The inference must be made that in these 6 cases the fundi were the better guide. Conversely we find 3 cases in which the pressures were above 250 mm. and the optic nerves appeared normal. Consequently it is impossible in this analysis to state that one test is consistently more delicate than the other as a guide to intracranial pressure.

That x-ray evidence of increased intracranial pressure is of value, no one will deny, but the time necessary to produce an effect visible in an x-ray film obviously renders this evidence of increased cerebral pressure somewhat different from that afforded by spinal fluid pressure determination or the examination of the fundus oculi.

COLOR

The appearance of the fluid is recorded in 54 cases, omitting a few in which gross contamination with blood occurred at puncture. Forty-one are reported as clear and colorless, and 13 as yellow or slightly yellow. Clotting *en masse* as seen in the fluid below spinal cord tumors was not observed; in fact clotting was not mentioned in any case.

The following chart gives the occurrence of xanthochromic fluids:

<i>Subtentorial tumors</i>		<i>cases</i>
Acoustic neuroma.....		5
Glioma.....		1
Arachnoid fibroma.....		1
<i>Supratentorial tumors</i>		
Glioma {	frontal.....	3
	temporal.....	3

It will be noted that the subtentorial tumors give a disproportionate number of yellow fluids, and further that 5 of the 8 acoustic neuromata furnish more than a third of the yellow fluids.

While the causation of xanthochromia is still a matter of debate, it may be mentioned that these fluids showing a yellow color also for the most part showed the highest protein values.

PROTEIN

A quantitative estimation of total protein (*i.e.*, albumins and globulins) was made by the Denis method of sulphosalicylic acid precipita-

TABLE IX

PROTEIN CONTENT OF LUMBAR FLUID IN THE DIFFERENT GROUPS, ABOVE AND BELOW HIGH NORMAL VALUE (40 MG. PER 100 CC.)

	NUMBER OF CASES ABOVE NORMAL	NUMBER OF CASES BELOW NORMAL
<i>Subtentorial:</i>		
Acoustic neuroma.....	8	0
Glioma.....	3	5
Arachnoid fibroma.....	3	1
Angiosarcoma.....	1	0
Cholesteatomatous cyst.....	0	2
Other cysts.....	2	2
Chronic meningitis.....	1	0
<i>Supratentorial:</i>		
Frontal.....	5	0
Glioma { Temporal.....	10	0
Parietal.....	2	2
Occipital.....	1	0
Meningeoma.....	1	2
Pituitary.....	1	1
Pineal.....	2	0
Metastatic carcinoma.....	1	0
Osteogenic sarcoma skull.....	1	0
Arachnoid cyst.....	5	3
Cholesteatomatous cyst.....	2	0
Totals.....	49	18

tion, and figures on all 67 cases are available for study. Less accurate tests with alcohol and ammonium sulphate were regularly made, and also an occasional Pandy test, but these are far less dependable and are therefore not analyzed.

With the sulphosalicylic acid method the upper limit of normal has

been placed at 40 mgm. of protein per 100 cc. of fluid. Table IX gives a concise idea of the occurrence of normal and abnormal fluids with regard to protein content.

Forty-nine cases, or 73 per cent of all cases, show an excess of protein in the lumbar fluid, the highest titer being 414 mgm. One group stands out from the others in a striking manner as regards high protein; of the 8 cases of acoustic neuroma, 7 gave values over 200 mgm., a uniform finding not approached by any other group of this series. This fact was especially striking because other tumors and cysts of as large size below the tentorium and much larger when above seldom gave such high readings. In fact, a large glioma, invading both frontal lobes and the caudate nucleus on one side and reaching to the ventricle gave 250 mgm., a reading less than most of the much smaller acoustic neuromata. The inference to be drawn is that the position and character of the acoustic neuroma must be of chief significance in determining the protein content of the fluid.

While it is not apparent from a study of the table, an analysis using 60 mg. as the dividing line would place most of the cysts on the "normal" side, for the protein values of fluids from cases with cysts usually stand just above normal.

CELLS

Cells were counted in the ordinary blood counting chamber, and it is the custom at this hospital to make a differential count at the same time by using acetic acid or Unna's blue to bring out the nucleus, employing the high dry objective of the microscope both for differential and actual count. The cells in these cases have been uniformly listed as lymphocytes and large mononuclear cells. Polymorphonuclear leucocytes were seen in one fluid only, but as another fluid from the same case failed to show them some doubt should be cast on this isolated finding. It is possible that tumor cells have passed unrecognized by this technique, but the cell count is probably not far from correct.

Sixty-two fluids from 58 cases are available for comparison. Only 12 cases yielded fluids with more than 5 cells per centimeter. While it is reasonable to consider 5 cells as abnormal, one does not attach much significance to a cell count of less than 10 per cubic millimeter; using this figure as a criterion we have but six cases presenting cell counts worthy of consideration, as follows:

- (1) Pinealoma: 3 fluids, showing respectively 15, 18 and 21 cells.
- (2) Glioma, extensive, both frontal lobes, with degeneration: 4 fluids showing 9, 12, 15 and 45 cells.
- (3) Glioma of cerebellum, with cystic degeneration: 27 cells.
- (4) Glioma, extensive, right cerebral hemisphere, with cystic degeneration: 3 fluids showing 1, 33 and 50 cells.
- (5) Fibrosarcoma, left cerebello-pontine angle: 41 cells.
- (6) Osteogenic sarcoma of skull: 18 cells.

Speculation as to the significance of cells in these cases is of interest. The three gliomata were large, and all showed cystic degeneration, in which it is common to find cellular exudate; in fact in case 2 puncture of the gliomatous cyst yielded so many cells that abscess was at one time suspected. It is therefore reasonable that in cystic degenerative gliomata the adjacent subarachnoid space should be the seat of low-grade inflammation, and that the products of such focal aseptic meningitis should find their way into the spinal fluid. Reasoning as to the origin of the cells in the three other cases is less profitable as two were seen only at operation and the third died and came to autopsy at another hospital; in this last case however soft friable tumor was found largely filling lateral and third ventricles, and was only recognized as of pineal origin by the microscopic study; it appeared to the examiner more than likely that cells should have floated off into the fluid from the tumor.

SUGAR

Quantitative sugar determinations were made by a modified Folin-Wu method in 24 cases, with the results briefly shown as follows:

Subtentorial (11 cases).....	53 to 82 mgm. per 100 cc.
Supratentorial (13 cases).....	44 to 82 mgm. per 100 cc.

Only one of the whole number of sugar determinations could be considered as abnormally low, and none as higher than normal limits. Therefore no significance is attached to sugar in these cases.

GOLDSOL REACTION

The gold chloride reaction of Lange has been considered by some writers as of great diagnostic importance in brain tumor. In this study the goldsol test has been systematically carried out and curves are available in 78 fluids taken from 62 cases. A large number of reactions are entirely negative, and many more show such slight color

change that they are considered normal. In fact only 15 curves were obtained in these 78 tests which could reasonably be considered as pathological. Because of the supposed importance of the goldsol test in diagnosis of brain tumor these figures are given in table X. To this table are added the protein figures, as it is generally thought that there is a certain relation between protein content and gold curve.

TABLE X
ABNORMAL GOLDSOL REACTIONS

	GOLD CURVE	TOTAL PROTEIN
<i>Subtentorial tumors and cysts: 8 of 25 cases (32 per cent abnormal)</i>		
		<i>mgm. per 100 cc.</i>
Acoustic neuroma.....	1113332000	400
Acoustic neuroma.....	2224433100	267
Acoustic neuroma.....	0000123221	414
Acoustic neuroma.....	0012333000	276
Acoustic neuroma.....	4554555322	334
Acoustic neuroma.....	2222332100	276
Cyst, cerebello-pontine angle.....	0122211000	138
Gliomatous cyst, cerebellum.....	1234221000	24
<i>Supratentorial tumors and cysts: 7 of 37 cases (16 per cent abnormal)</i>		
Glioma, frontal.....	0000122111	334
	0001121100	348
Glioma, occipital.....	1123200000	63
Glioma, parietal.....	0001111221	138
Glioma, parietal.....	0122100000	70
Glioma, frontal.....	0000130000	250
Pinealoma.....	1121000000	39
	2222110000	53
	1221000000	44
Arachnoid cyst of cortex.....	0123210000	44
	1121110000	43

Analysis is not difficult. Not one of these reactions can possibly be considered as pathognomonic. Most of the curves resemble the findings in neurosyphilis, although similar reactions are seen in other exudative and degenerative diseases of the nervous system.

SUMMARY AND DISCUSSION

Analysis of individual tests as given above, while showing abnormal findings frequently, still leaves the impression that many fluids in brain tumor are normal. When all of the tests in a given case are studied together quite a different idea is obtained. In the subtentorial group of 28 cases *only 1 case presents a normal fluid in every particular*, although 7 are negative with the single exception of abnormal pressure studies, block being demonstrated in 5 of them. Likewise in the supratentorial group of 39 cases *only 4 fluids are entirely negative* (in cases where all the data are at hand) and again 3 others are negative except for high fluid pressure.

The analysis demonstrates very clearly the importance of careful pressure and dynamic study and of accurate quantitative protein determination, for in these two tests is seen the greatest abnormality in tumors and cysts of the brain. Cytology, sugar estimation and goldsol readings play a minor rôle as diagnostic criteria in our cases.

One might summarize by saying that tumor of the brain should be strongly suspected if the spinal fluid pressure be over 300 mm., and contain twice normal protein, without as a rule cell increase, and with or without an abnormal goldsol reading; that evidence of block, as shown best by combined ventricular-lumbar puncture, is of the utmost significance as demonstrating obstruction between ventricles and spinal subarachnoid space. Xanthochromia when present is an occasional finding of significance.

The question arises whether the evidence obtained is worth the well-known risk of lumbar puncture in cases of increased intracranial pressure. If the findings of brain tumor were pathognomonic the answer should probably be in the affirmative. Unfortunately other conditions give similar fluid syndromes, notably uremia and some forms of cerebral hemorrhage. At best then one usually learns what is probably already apparent from a fundus examination, namely, that the patient has increased intracranial pressure, which *may* be due to brain tumor.

There are unquestionably cases in which an examination of the spinal fluid is highly desirable, even when increased intracranial pressure is strongly suspected or even assured. In cases with normal fundi or the slightest papilloedema little or no risk is apparently run by lumbar puncture and the pressure studies and fluid analysis are of

value; also in cases when brain abscess or sinus thrombosis or syphilitic meningitis are under suspicion it is of vital importance to examine the fluid. In these cases lumbar puncture is justifiable, although when practicable the combined method is to be recommended as safer. In cases of obvious tumor with high degree of choked disc, especially if below the tentorium, the writer feels that the information likely to be gained is not worth the risk of lumbar puncture.

DISCUSSION

The following question submitted to Dr. Ayer before the Commission, together with the answers to it, is here reported verbatim.

DR. J. M. NIELSEN: Is not lumbar puncture performed only for the purpose of determining the intra-arachnoidal pressure and without the withdrawal of fluid a perfectly safe procedure?

DR. AYER: Absolutely not. Because the puncture has opened a hole in the dura from which the fluid can flow if the pressure be high enough. The fact that the hole in the dura is patent was demonstrated in connection with Dr. Weed some years ago. We put lamp black into the cistern of a cat, following cistern puncture. The animal was allowed to run about afterwards and then sacrificed. Much of the lamp black was found between the neck and back muscles. I believe that lumbar puncture headaches are also caused by leakage of cerebrospinal fluid subsequent to the withdrawal at puncture.

CHAPTER XIV

CONVULSIVE SEIZURES DUE TO A GENERAL RISE OF INTRACRANIAL PRESSURE

WALTER M. KRAUS, M.D.

ON FIRST analysis, it might be assumed that an increase of intracranial pressure is in itself an adequate cause of convulsions. A more careful consideration leads to the opposite opinion.

The increase of pressure may be demonstrated by simple observation of increased pressure on lumbar puncture, or by a manometric estimation. This latter is of course the more accurate of the two methods. Choked discs are usually certain evidence of increased intracranial pressure. However, in some cases of epidemic encephalitis, choked discs are found which may not be associated with a rise in pressure parallel to the appearance of the discs. The choking is probably due to blocking the pia-arachnoidal sheaths of the nerves themselves. The other signs said to indicate increased intracranial pressure such as bradycardia, headache, nausea, vomiting and cranial nerve paralysis are not certain evidence. Examination of the skull by x-rays may show evidence of increased pressure. However, for the purpose of discussion, all of these manifestations or findings are inadequate to assist in reaching a decision. What is a *sine qua non* is a very thorough post-mortem examination of the brain, preferably by serial whole brain sections.

There must be post-mortem evidence to show at least that there is no damage which affects the pathway from the pre-Rolandic area to the segmental effector cells. This is the minimum. What the maximum may be will depend upon a much more intimate knowledge of the parts of the brain which are concerned in the initiation of convulsions. All convulsions are not due to involvement of the cortico-fugal paths alone.

Certainly, when disease affects those parts of the brain which are capable of precipitating convulsions, the convulsions cannot be attributed to increased intracranial pressure alone.

THE EFFECT OF INCREASED INTRACRANIAL PRESSURE IN VARIOUS DIS-
ORDERS OF THE NERVOUS SYSTEM

When convulsions occur in patients having increased intracranial pressure and suffering also from an infection, an intoxication or an injury, the increased pressure cannot be assumed to be the cause of the convulsions; the disease itself is the cause. The great number of such cases without convulsions illustrates this. Cases of acute septic meningitis with greatly increased pressure are concrete examples of the infectious group. In intoxications, there is no rule that convulsions occur, whether pressure be increased or not. In injury, such as fracture of the skull, the increase of pressure is certainly not a cause of convulsions, when they do occur. Irritation by hemorrhage or depressed bone is at fault in most cases.

In rarer diseases of little known etiology, the same, I believe, holds true. Increased pressure has not been demonstrated in enough of these to warrant more than a belief.

In obstructive hydrocephalus experimentally produced in dogs Dandy and Blackfan (1) stated that no irritative phenomena resulted, nor are convulsions common or frequent in cases of obstructive hydrocephalus in man.

Neoplasms and aneurysms are frequently associated with both convulsions and increased intracranial pressure. In order to attribute the one to the other, a very thorough pathological examination is required as I have above emphasized. Tumors are much more widely spread than they seem to be either from clinical or operative observations.

Seven cases of tumor of the brain examined as I have outlined above and taken from the collection at the Laboratory of Neuropathology at Montefiore Hospital have been ruled out as evidence that convulsions are due to increased intracranial pressure, because in all, the cortico-segmental path was either severely diseased or compressed.

In tumors or aneurysms of the posterior fossa which are so often associated with increased intracranial pressure convulsions are rare, which is added evidence for the opinion that increased intracranial pressure is not an adequate cause of convulsions. Were it, convulsions would be the rule in tumors of this region.

INCREASED INTRACRANIAL PRESSURE AS A PREDISPOSING FACTOR,
RATHER THAN A CAUSE OF CONVULSIONS

Elsberg and Pike (2) have shown experimentally that when intracranial pressure is decreased by injection of hypertonic solutions, the dose of absinth which will produce a convulsion under usual experimental conditions is no longer sufficient. It must be greatly increased. Per contra, if intracranial pressure is increased, the dose needed is much less than that needed under usual experimental conditions. In other words, increased intracranial pressure is a definite influence predisposing to convulsions. If a second factor which may produce convulsions be introduced, it will do it most easily when pressure is high.

Stevenson, Christensen and Wortis (3) have stated that intracranial pressure is raised during sleep. This suggests a possible causal relation between increased intracranial pressure and nocturnal convulsions (epilepsy). One wonders whether the rise in pressure predisposes the patient to the convulsion.

These investigations bring us back to the original main discussion, given a brain having within it an expanding growth as a tumor or aneurysm, will a fairly rapid rise in pressure predispose to a convulsion? I believe that it will, provided that the growth is located in a place from which convulsions may be caused.

In rapid compression by hemorrhage, either from arteries diseased by neoplasms or from arteries diseased by sclerosis, convulsions are not the rule at all.

In slow compression of the brain, it behaves like a sponge, as I have often found in examining large sections of such cases. The brain may be compressed in many of its parts without a single clinical manifestation. Convulsions are not necessarily sequelae. Thus in neither type of compression are convulsions usual sequelae.

CONCLUSIONS

1. Increased intracranial pressure alone does not produce convulsions.
2. When increased intracranial pressure becomes associated with another disorder which under normal or nearly normal pressure conditions will not produce convulsions, it may so change intracranial conditions so as to cause the other disorder to precipitate convulsions.

Under such circumstances, two things are necessary, the primary disorder and the superimposed increase of pressure.

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CHAPTER XV

INTRACRANIAL PRESSURE AND THE SUSCEPTIBILITY OF ANIMALS TO EXPERIMENTALLY PRODUCED CONVULSIONS¹

FRANK H. PIKE, M.D.

WITH REMARKS ON THE SIGNIFICANCE OF THE RESULTS OF THE EXPERIMENTS FOR THE STUDY OF THE NATURE OF CONVULSIVE SEIZURES IN MAN

CHARLES A. ELSBERG, M.D.

IN THE following series of experiments, the effects of variations of intracranial pressure upon the susceptibility of animals to absinth convulsions were studied in two ways:

1. Intracranial pressure was raised or lowered by the intravenous injection of distilled water or of concentrated solutions of sodium chloride or of glucose.² Some of the animals were bled after the fluid had been injected.

2. Intracranial pressure was raised by the introduction between the calvarium and the dura of foreign bodies of a greater or less size.

In this report, the experimental results are presented by Dr. Pike,³ while the general remarks on the possible correlation of the results with clinical symptoms in man have been added by Dr. Elsberg.

The technique of the preparation of the animal for the experiments did not require etherization but only local anesthesia. The animal was placed back downward on the operating table; two towels were passed around its body and fastened on the under side of the table with clamps or safety pins—one towel being passed around the neck and the other just back of the forelimbs. The four limbs were

¹ From the Laboratory for Experimental Neurology of the College of Physicians and Surgeons, Columbia University, and the Division of Neuro-Surgery of the Neurological Institute, of New York. Work done under a grant from the Commonwealth Fund to the Neurological Institute, for Research on Epilepsy.

² These experiments have been published in detail in: Elsberg, C. A., and Pike, F. H.: *American Journal of Physiology*, 1926, lxxvi, 593-97.

³ In order to save space, the general results of the experiments will be given with only a few of the protocols.

fixed in the usual manner by means of cords, and if the towels around the animal's body were properly applied, the cords that held the limbs could be left loose enough to allow of considerable freedom of movement.

The right hind leg was then held securely while about 2 cc. of a solution of novocain were injected into Scarpa's triangle along the course of the internal saphenous nerve close to its emergence from the abdominal wall. A few minutes later, the skin was cut with scissors from about the knee to the external abdominal ring. This can usually be done without any protest on the part of the animal. If there was evidence of pain, more novocain was injected and some minutes allowed to elapse before going on with the exposure of the vein. As soon as the anesthesia was complete, the nerve was dissected out close to its emergence and cut. The internal saphenous vein, and the femoral vein above the junction of the saphenous with the profunda femoris were cleared of fascia and a long course of a large vein was then available for repeated injections.

The limb should be held by an assistant at the time of making the injection, as any movement of the animal is a disturbing element. Fluid may be introduced by passing a hypodermic needle through the wall of the vein. A syringe or a perfusion bottle may be used, depending upon the quantity of fluid to be injected. Blood may be withdrawn either from the vein or from the femoral artery. As the field is desensitized, there are no confusing responses of reflex origin, to say nothing of the more important factor of freedom of the animal from pain.

I. THE EFFECT OF HEMORRHAGE UPON THE SUSCEPTIBILITY TO ABSINTH

Merely by way of recapitulation, we may say (1) that the intravenous injection of large volumes of distilled water or salt solution of low concentration, increases the susceptibility of cats to absinth, both as regards the minimal convulsing dose and the lethal dose; while (2) the injection of smaller quantities of concentrated solutions of sodium chloride or of sugar, decreases the susceptibility.

There is reason to believe that solutions of low or of high concentration introduced into the circulation lead to an increase or a decrease respectively of the intracranial pressure, due to osmotic flow from blood to cerebrospinal fluid or vice versa.

The question arises, what will be the effect of the intravenous injection of large volumes of fluid of the same osmotic concentration as the blood? Less osmotic interchange between cerebrospinal fluid and blood would be expected than where solutions of lower or higher concentration are used.

The actual results of the intravenous injection of fluid-isotonic, or nearly so, with the blood are similar to the results which follow the

injection of fluid of low concentration, as is shown by the following experiment:

Experiment 434. Cat, weight $7\frac{1}{2}$ lbs., 300 cc. of normal saline solution injected into femoral vein.

<i>Time</i>	<i>Amount of absinth injected</i>	<i>Result</i>
3.17 p.m.	0.15 cc. or 0.02 cc. per pound.	Contraction of pupils, twitches of muscles.
3.27 p.m.	0.19 cc. or 0.025 cc. per pound.	Twitches, cries.
3.37 p.m.	0.22 cc. or 0.03 cc. per pound.	Twitches.
3.47 p.m.	0.25 cc. or 0.035 cc. per pound.	Thrombus in vein.
3.57 p.m.	0.22 cc. or 0.03 cc. per pound.	Severe convulsion, severe twitches, unequal pupils.
4.00 p.m.	80.0 cc. of blood removed from femoral artery.	
4.07 p.m.	0.22 cc. or 0.03 cc. per pound.	Violent convulsions, pupils widely dilated.
4.15 p.m.		Death.

General result. The intravenous injection of a large quantity of normal salt solution increased the susceptibility of the animal to absinth, and the dosage which merely produced convulsions before the animal was bled, was lethal afterward.

Hemorrhage alone, without previous injection of fluid into the circulation, lowers the lethal dose of absinth, when the blood withdrawn ranges from about one per cent to one and one-half per cent of the body weight of the animal (33 cc. to 50 cc. in a cat of three kilos).

Experiment 436. Cat, weight $6\frac{1}{4}$ pounds.

<i>Time</i>	<i>Procedure</i>	<i>Result</i>
2.48 p.m.	Injection of 0.18 cc. or 0.03 cc. per pound, of absinth.	Convulsion not severe.
2.52 p.m.	50 cc. of blood withdrawn from vein.	
3.04 p.m.	Injection of 0.18 cc. or 0.03 cc. per pound, of absinth.	Convulsion, marked respiratory effects, muscular twitches.
3.07 p.m.		Death.

Loss of even a larger amount of blood (60 cc. in a cat of three kilos) followed by an intravenous injection of about twice as much (130 cc.) of 0.9 per cent sodium chloride solution, did not greatly affect the minimal convulsing dose of absinth, but did, apparently, raise the lethal dose. The following experiment will serve as an illustration:

Experiment 437. Cat, weight $6\frac{1}{2}$ pounds,

<i>Time</i>	<i>Procedure</i>	<i>Result</i>
3.15 p.m.	Injection of absinth. 0.19 cc. (0.035 cc. per pound).	Severe convulsion.
3.21 p.m.	60 cc. of blood withdrawn.	Respirations rapid, pupils moderately dilated.
3.35 p.m.	Injection of absinth 0.13 cc. (0.02 cc. per pound).	Muscular twitches.
3.45 p.m.	Injection of absinth 0.025 cc. per pound.	Muscular twitches.
3.50 p.m.	Injection 0.03 cc. per pound.	Severe prolonged convulsion, muscular twitches, pupils dilated.
3.55 p.m.	Injection of 130 cc. of saline solution.	
4.10 p.m.	Injection of 0.19 cc. of absinth (0.03 cc. per pound).	Severe convulsion, muscular twitches, nystagmus.
4.22 p.m.	Injection of 0.04 cc. per pound.	Severe convulsions for seven minutes.
4.35 p.m.	Injection of 0.05 cc. per pound.	Severe muscular twitches.
4.44 p.m.		Death.

The results in the experiments of which the last two just recorded are examples, are not at all clear. In the case of loss of a small amount of blood, it is possible that, with the same dosage of absinth to the pound of body weight, the concentration of absinth in unit volume of blood, was increased. This statement would not apply with equal weight in the cases where a large amount of fluid had previously been introduced into the circulation. In the latter animals, not only was the minimal convulsive dose of absinth lowered, but after the withdrawal of blood, the dose of this substance large enough to cause a fatal convulsion had to be increased.

II. THE INTRODUCTION INTO THE CRANIAL CAVITY AND OVER THE MOTOR AREA, OF VASELINE, PARAFFIN, OR LAMINARIA TENTS, FOLLOWED BY INJECTIONS OF ABSINTH

1. *The effects of the extradural injection of vaseline or paraffin*

As is well known, the intravenous injection of normal or hypotonic or hypertonic solutions is followed by a general increase or decrease of intracranial pressure affecting both sides of the brain alike. The introduction of a substance extradurally, might be expected to cause a more localized increase as well as a certain amount of general rise in

pressure conditions within the cranial chamber. The local increase of pressure might be expected to manifest itself by some difference in the responses of the two sides of the body to the intravenous injection of a convulsing substance such as absinth.

To gain information on this aspect of the subject, a series of experiments was performed in which vaseline or paraffin was injected into the cranial cavity on one side through a small opening in the bone. As soon as the animal had recovered from the anesthesia, injections of absinth were given. The following was a typical experiment:

Experiment 388. Cat, weight $9\frac{1}{4}$ pounds. Injection of 2 cc. of paraffin extradurally over the left frontal area. The only apparent result was that the left pupil became dilated.

<i>Time</i>	<i>Amount of absinth injected</i>	<i>Result</i>
2.34 p.m.	0.195 cc. (0.02 cc. per pound).	Marked respiratory disturbance.
2.44 p.m.	0.195 cc. (0.02 cc. per pound).	Two severe convulsions.
2.54 p.m.	0.195 cc. (0.02 cc. per pound).	Marked nystagmus.
3.06 p.m.	0.25 cc. (0.025 cc. per pound).	Muscular twitches of left ear and left eyelid and of right hind limb. Left pupil greater than right. Left external strabismus.
3.17 p.m.	0.25 cc. (0.025 cc. per pound).	
3.25 p.m.	0.25 cc. (0.025 cc. per pound).	Muscular twitches of left ear and left eyelid; tonic extension of right foreleg. Tendon reflexes on left more active than on right.
3.35 p.m.	0.25 cc. (0.025 cc. per pound).	Severe generalized convulsion.
3.39 p.m.		Death.

Post mortem examination showed that the paraffin lay over the left motor area and part of the parietal region, and that there was some extradural hemorrhage.

The increase of general susceptibility to absinth, as indicated by the small lethal convulsing dose, was more marked than the difference in deportment of the two sides of the body during the convulsions. The results of the experiments were, however, sufficiently encouraging to warrant the effort to cause a more strictly localized increase of pressure or irritation. Accordingly, a piece of laminaria tent was introduced into the cranial cavity over the motor area in a number of animals. The results obtained in the experiments are given in the following section of this paper.

2. *The effects of the introduction of laminaria tents over one motor area*
(19 experiments)

The idea of the use of tents arose from some earlier experiments of J. Gordon Wilson and F. H. Pike on the introduction of pieces of sterilized tupelo tent into the posterior cranial fossa of cats. With the gradual swelling of the tents, the cats, in these earlier experiments, regularly died within twenty-four hours.

In the present series of experiments, a small piece of tent was introduced extradurally as nearly over the cruciate fissure of one cerebral hemisphere as possible.

Under aseptic precautions the skin of the vertex was incised in the median line from a point just back of a line passing above the margins of the orbits to about the mid point of the vertex of the cranium. One skin flap, usually that on the left side, was pulled over to the side, without cutting it free from the subcutaneous tissues, until the anterior attachment of the temporal muscle came into view. The temporal muscle was then cut free from the bone at the angle where the vertical or anterior border joins the superior border, and the bone was exposed for about 1 cm. below the upper border of the muscle.

A small hole, 2 to 3 mm. in diameter was drilled in the bone and a piece of tent about $\frac{1}{2}$ inch long was driven into the skull, so that the part which projected into the cranial cavity was $\frac{1}{4}$ to $\frac{3}{8}$ inch in length. The wound was then carefully closed by suture.

No immediate effects were observed when the animals recovered from the anesthesia, and usually no very apparent symptoms were noticeable during the first few days after the operation. Some weeks or months afterward, the only symptoms observed are some loss of facility of movement, especially in the forelimb of the side opposite to the lesion. For example, the cat may have difficulty in removing a piece of adhesive plaster placed over the eye of the side opposite the lesion, while the eye on the same side as that of the lesion is easily freed of adhesive tape.

At the autopsy on the animals, after they had been used for experiments, a cavity in the cerebral hemisphere 8 to 15 mm. in diameter, and 10 to 12 mm. deep may be found, formed by the enlarged piece of extradurally situated laminaria tent. Dependent upon the correct location of the tent, the cavity was almost exactly bisected by the line of the cruciate fissure; at other times the cavity lay a little further back, and sometimes it was entirely caudal to the cruciate fissure (see fig. 73).

The effect of such a lesion upon the susceptibility to absinth convulsions varies somewhat with the time that has elapsed between the introduction of the laminaria tent and the injection of the absinth.

If the animal is tested with absinth about one week after the foreign

body has been introduced into the cranial chamber, there is some difference in the character of the convulsive movements on the two sides of the body. They have more of a tonic character on the side opposite to that of the lesion and are more clonic on the same side. In this respect they resemble the responses to absinth seen a few days after the surgical removal of the cortical motor area.⁴

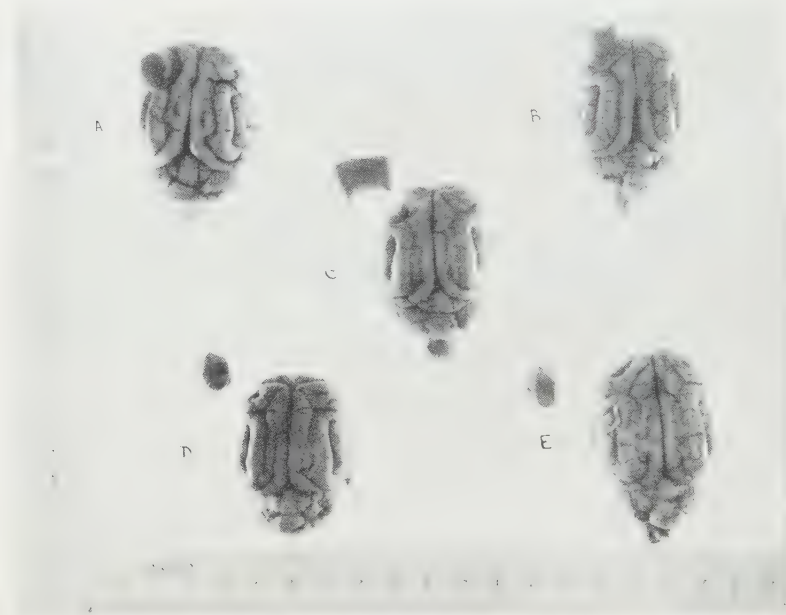


FIG. 73. Showing the location of the lesion after the introduction of a piece of laminaria tent over the left motor region. *A* and *B*, laminaria tent in situ; *C* and *E*, showing the lesion in the left cruciate area after the removal of the laminaria tents; *D*, a lesion not in the cruciate area due to a laminaria tent.

There is also a slight but distinct difference of the susceptibility of the two sides of the brain—convulsions or convulsive movements appearing on the same side as the lesion, after somewhat smaller doses of absinth. The general susceptibility of the animal seems increased, as the minimal convulsing dose is somewhat smaller than in normal animals. The same is true of the lethal convulsing dose of absinth.

⁴ Pike, F. H., and Elsberg, C. A.: *American Journal of Physiology*, 1925, lxxii, 337.

When a somewhat longer time—five or six weeks—is allowed to elapse between the insertion of the laminaria tent and the injections of absinth, some differences in the reactions were observed:

The first effects of injections of small amounts of absinth—less than the minimal convulsing dose—may be only an increase of reflex irritability on the side opposite to that of the lesion. Just before the minimal convulsing dose is reached, the animal may turn itself away from the side of the lesion, *i.e.*, toward the right when the lesion is in the left motor area. There may be a marked clonus of the hind foot on the side opposite to that of the lesion when the patellar tendon is tapped. Convulsive twitches, clonic in type, may appear first in the limbs opposite to the side of the lesion but later they occur on both sides.

All these minor symptoms may appear before the dose of absinth has been large enough to cause sweating of the pads of the feet—indicating a greater susceptibility of the cerebrospinal than the autonomic system.

The reflexes show some important changes. The patellar reflex on the side opposite the lesion is more active than that of the other side, and crossing of the reflex to the opposite side, *i.e.*, from left to right but not from right to left when the lesion is in the left motor area. There may be a spread of the reflex from the hind to the fore limb on the side opposite to the lesion. We have observed, also, reflex responses of both fore limbs on percussion of one hind limb, *i.e.*, on tapping the left patellar tendon when the lesion is in the left hemisphere, with an approach to clonus in the forelimb contralateral to the lesion.

When the interval between the insertion of the laminaria tent and the injections of absinth is still larger—*i.e.*, from six to twelve months—the spread of the reflexes may be from the side opposite to that of the lesion to the limb on the same side as the lesion, *e.g.*, from right patellar to left but not from left to right when the tent is over the left hemisphere. The toes of the right foot may be widely spread apart, but the clonus now appears in the left hind foot (on the same side as the lesion).

The pupil on the same side of the lesion may be under the influence of absinth, consistently larger than the other one, with muscular twitches in the forefoot of the same side but no movements on the other side. This represents a reversal of the findings in those experi-

ments in which the absinth injections were made only a few weeks after the insertion of the laminaria tent.

The findings two years after the laminaria tent had been inserted were much the same as those described in the preceding two paragraphs. The minimal dose of absinth necessary to cause a convulsion was slightly larger, but this as well as the lethal convulsing dose were still small as compared with the minimal doses for the same effect in normal animals.

The reflexes were usually found to be more active on the same side as the lesion, and the toes more spread out on the side opposite to that of the lesion. Clonus was more easily elicited in the hind foot on the same side as the lesion as in the following protocol:

Experiment 464. Cat, weight 11 pounds. Craniotomy on left and insertion of laminaria tent, April 15, 1926. Absinth injections June 6, 1928.

<i>Time</i>	<i>Amount of absinth injected</i>	<i>Result</i>
2.56 p.m.	0.22 cc. (0.02 cc. per pound).	Nystagmus; rapid respiration; all tendon reflexes hyperactive.
3.01 p.m.		Pads of feet moist.
3.10 p.m.	0.275 cc. (0.025 cc. per pound).	Reflexes on left more active than those on right.
3.20 p.m.	0.275 cc. (0.025 cc. per pound).	Transient clonus in left hind leg.
3.30 p.m.	0.30 cc. (0.0275 cc. per pound).	Clonic twitches of muscles on both sides of body, more easily elicited on left.
3.35 p.m.		Twitches on left side followed by twitches on both sides. On tapping sole of right foot there is clonus of left hind foot.
3.44 p.m.	0.36 cc. (0.03 cc. per pound).	Toes of right foot spread apart. Tonic extension followed by clonic twitches.
3.56 p.m.		Death.

In all of the animals, during the convulsions from absinth, ocular nystagmus and bilateral dilatation of the pupils was very frequent. Perspiration appeared on the pads of the feet, sometimes more marked on the side opposite to the lesion. Dilatation of the stomach was usually observed.

In some animals, in which the chest was opened soon after death, the left ventricle of the heart was not in rigor as is usually found after death in experimental animals.

These findings together with occasional pilomotor activity, as shown by the bristling of the hair on the back, indicate that there is a participation of the sympathetic nervous system in the responses to absinth. To this, the flabbiness of the left ventricle of the heart found after death seems an exception.

SIGNIFICANCE OF THE RESULTS OF EXPERIMENTS FOR STUDY OF THE
NATURE OF CONVULSIVE SEIZURES IN MAN

The interpretation of the results of the experimental researches described by Dr. Pike, and their possible significance as regards convulsive seizures in man, offer a wide field for speculation. The experiments clearly demonstrate that changes in intracranial pressure have an influence upon the susceptibility of animals to artificially produced convulsions.

The increase of intracranial pressure produced by the injection of hypotonic solutions or of large quantities of fluid isotonic with the blood serum is due to swelling of the brain itself or to the increase in volume of intracranial fluid, or to both. The result of such a rise of pressure within the cranial chamber, is a diminution of the total volume of intracranial blood and especially of the blood in the cortex of the brain as shown by the experiments of Forbes and Wolff and of Kubie and Hetter, and there is much to support the belief that there is an anemia and anoxemia not only of the cortex but of the entire substance of the brain.⁵

An increase of intracranial pressure artificially brought about by other means, as, for example, by the introduction into the cranial cavity of a material which gradually swells up and occupies more and more space—such as a piece of laminaria tent—will have a similar effect. In this instance, however, there is not only a general increase of pressure and a diminution of the total blood volume within the cranial cavity, but for a time at least, in the region occupied by the foreign body, a local rise in pressure and a more localized interference with the blood supply in the part directly pressed upon by the laminaria tent.

The intravenous injection of hypertonic solutions is followed by a

⁵ This has been shown by Stewart, Guthrie and Pike, and later by Elsberg and Stookey, in experiments in which a temporary anemia of the brain produced by clamping off the carotid, subclavian and vertebral arteries for a period, was followed by convulsive seizures.

diminution of intracranial pressure as originally demonstrated both in animals and in man by Weed and McKibben. If the amount of concentrated fluid is not too large, the total volume of intracranial blood and the blood supply of the brain itself are increased.

From all of these facts, it is reasonable to believe that the changes in susceptibility of animals to artificially produced convulsions, when intracranial pressure is either lowered or raised, are intimately connected with the variations in the blood supply to the nervous tissues.

The facts demonstrated by some of our experiments that anemia brought about by bleeding the animal will increase the susceptibility to absinth convulsions and that this heightened susceptibility due to hemorrhage can be again diminished by intravenous injection of normal saline solution, give further support to the belief that anemia, and anoxemia play an important rôle in the occurrence (but not the origin) of the explosive phenomena produced in the animals.

Of no little interest are the results of the experiments in which laminaria tents were introduced over the motor area of one hemisphere, and the animals tested out for their susceptibility to absinth, after varying periods of time. Within about the first week of the operation, the hemisphere on the same side as the laminaria tent seemed to be less irritable, so that more marked clonic and tonic movements occurred in the limbs of the side of the lesion and convulsions or convulsive movements could be produced from the normal hemisphere by doses of absinth that did not affect the opposite side at all.⁶

After five to six weeks, however, the condition of affairs changed, the side of the brain compressed by the piece of laminaria became more susceptible, clonic movements occurred first in the limbs controlled by the affected hemisphere, and only when larger doses of absinth were used, did the convulsions affect both sides of the body.

⁶ This is in accordance with what is seen in animals in whom a convulsing drug is injected soon after a cranial trauma such as the extirpation of the motor cortex of one or both sides of the brain. In these "acute" experiments, clonic convulsions can usually not be produced at all and this has led some investigators to the wrong conclusion that an intact cortex was necessary for the production of a typical convulsive seizure.

It is well known, also, that clinically in man, after a severe trauma of the skull and brain, the tendon reflexes may be lost entirely for a number of days, and that, after an operation upon the brain in an epileptic, convulsive seizures may not reappear for a short or longer period.

Finally, six months to two years after the laminaria tent had been introduced, at a period when the foreign body had long remained of a constant size, the motor mechanisms of the hemisphere on the side of the intracranial lesion were no longer more susceptible than those of the other side of the brain. It seemed that a readjustment had taken place. All of the animals, however, after the "acute" period of about one to two weeks, remained more susceptible, so that the minimal convulsing dose of absinth was well below that necessary to produce an effect in a normal unoperated animal, and this heightened susceptibility was still present several years after the introduction of the laminaria tent.

All of these facts may well have importance with reference to convulsive seizures that occur in the human being. There is much to support the belief that, in the final analysis, convulsive seizures in man, of cerebral origin, are secondary to an interference with the normal blood supply to the epileptogenous areas—no matter where they are located. If this be so, the mechanism of convulsions due to a systemic disorder such as anemia, or to a local intracranial lesion such as a tumor, an inflammatory change, a cicatricial change following a trauma, a vascular alteration as in arteriosclerosis, or a change of unknown character, as in the disease called "epilepsy" is the same.

In one instance it is a poison, in another it is a scar which has disturbed the normal supply of fluid to the nerve cell, in another, the pressure of a neoplasm or a rise of intracranial pressure from some other cause has interfered with the circulation around the nerve cells. Spasm of the blood vessels in one or other part of the brain may bring about the same effect. If the anemia and anoxemia affect only one cerebral hemisphere or a part of it, as might occur from the pressure of a tumor or from a cicatrix after a trauma, then the convulsive seizures may be of the Jacksonian type.

A tumor far away from the motor areas of the brain, especially if located in a "silent" area, may cause a general rise of intracranial pressure, with a resulting relative anemia of the entire brain, so that if convulsive seizures occur, they are generalized and involve both sides of the body.

All of this gives no clue to the actual origin of convulsive seizures in man in the symptom complex which we call epilepsy. That for typical clonic and tonic convulsions, an intact motor cortex is not necessary seems certain from the results of many careful experimental

researches. The change that occurs in the nerve cells of some part of the brain brings about either an inhibition of some nervous activity, so that the convulsion is a "release" phenomenon or a "short circuiting," or the result is due to "irritation" and an "explosive" process. In some sense, therefore, every normal individual is, potentially, an "epileptic."

Much research will be necessary to solve the complicated problems which such a viewpoint presents.

That variations in intracranial pressure, and especially a rise in pressure, will increase the susceptibility of those individuals who—from whatever cause—are subject to convulsive seizures, is shown by the results of the experiments reported in this paper.

CHAPTER XVI

FUNCTIONAL AND ORGANIC ALTERATIONS FOLLOWING THE INTRODUCTION OF BLOOD INTO THE CEREBROSPINAL FLUID¹

CHARLES BAGLEY, JR., M.D.

THIS work has been done with the hope of producing experimentally lesions simulating those in humans resulting from the escape of a small amount of blood into the subarachnoid space.

Eighteen adult dogs (exact age unknown) and twenty-six puppies (5 litters) all less than ten days old were injected. An average pup from each litter was used as a control.

Whole blood to be injected was obtained from the leg vein of the adult dogs and the longitudinal sinus of the pups. Free mixture of the blood and cerebrospinal fluid was desired and the blood was slowly injected into the cisterna magna, in the subarachnoid space, over the cerebral hemisphere, and in a few instances, into the cerebral ventricles.

The work was started on adult dogs with frequent injections of from 0.5 to 2.5 cc. of blood. More could not be given in the cisterna magna without serious respiratory symptoms, but in a few instances, as much as 5 cc. was tolerated over the cerebral cortex. In the beginning when adult dogs were being used, it was thought that repeated injections at short intervals would be required to produce a disturbance comparable to that observed in humans with bloody cerebral spinal fluid; for this reason some of the earlier dogs received as many as six injections. In the later experiments with young pups it was found that a single injection would sometimes produce symptoms, and, therefore, most of the later pups received but one or two injections.

Ether anesthesia was used in the adult dogs. One-sixth grain of morphia was given hypodermically about half an hour before the

¹ From the Neurological Laboratory of the Henry Phipps Psychiatric Clinic, Johns Hopkins University, with the assistance of the Epilepsy Medical Research Fund.

ether administration. Chloroform without morphia was used in anesthetising the pups.

When the animals died or were sacrificed, autopsies were performed. To avoid possible injury of the meninges in the removal of the brain, the skull containing the brain was sectioned with a fine saw and then immersed in 10 per cent formalin. By this method any portion desired for photography or microscopic study could be exposed in the fresh state, and the entire brain easily brought into contact with the fixing fluid. The tissue was embedded in paraffin unless the dura was included in the blocks, in which case celloidin was used. Haematoxylin and eosin stain was used.

CLINICAL COURSE

Immediately after the injection, the adult animals were restless, spastic, and recovered from the narcosis very slowly. At times the spastic extremities were very active, in some cases the movements simulating running. At other times there were atypical convulsive seizures with frothing at the mouth. The following day the animals were usually dull but walked about the cage and took food. The dogs after the injections were kept under observation in the laboratory from one to three hours after which they were returned to the animal room. Daily visits were made to these animals and every few days they were brought into the laboratory and allowed to play about under observation from one to three hours. In this way it was possible to

FIG. 74. A. Frontal section through the brain of one of the control pups showing the normal ventricle to be very small.

B. Showing the dilated ventricle of adult dog 10 which received six injections of blood in the cisterna magna over a period of thirty-nine days and was sacrificed two days after the last injection.

C. The brain of pup 35 which received three injections of blood over the right cortex and two in the cisterna magna over a period of forty-two days and was sacrificed twenty-one days after the last injection.

D. The brain of pup 37 which received two injections of blood over the right cortex and two in the cisterna magna over a period of forty-two days and was sacrificed seven days after the last injection.

E. The brain of pup 45 which received one injection of blood in the cisterna magna and was sacrificed twenty-one days later.

F. The brain of pup 47 which received two injections in the cisterna magna over a period of seven days and was sacrificed ten days after the last injection.

G. The brain of pup 70 which received 1.25 cc. of blood in the cisterna magna and died sixty-two days later.

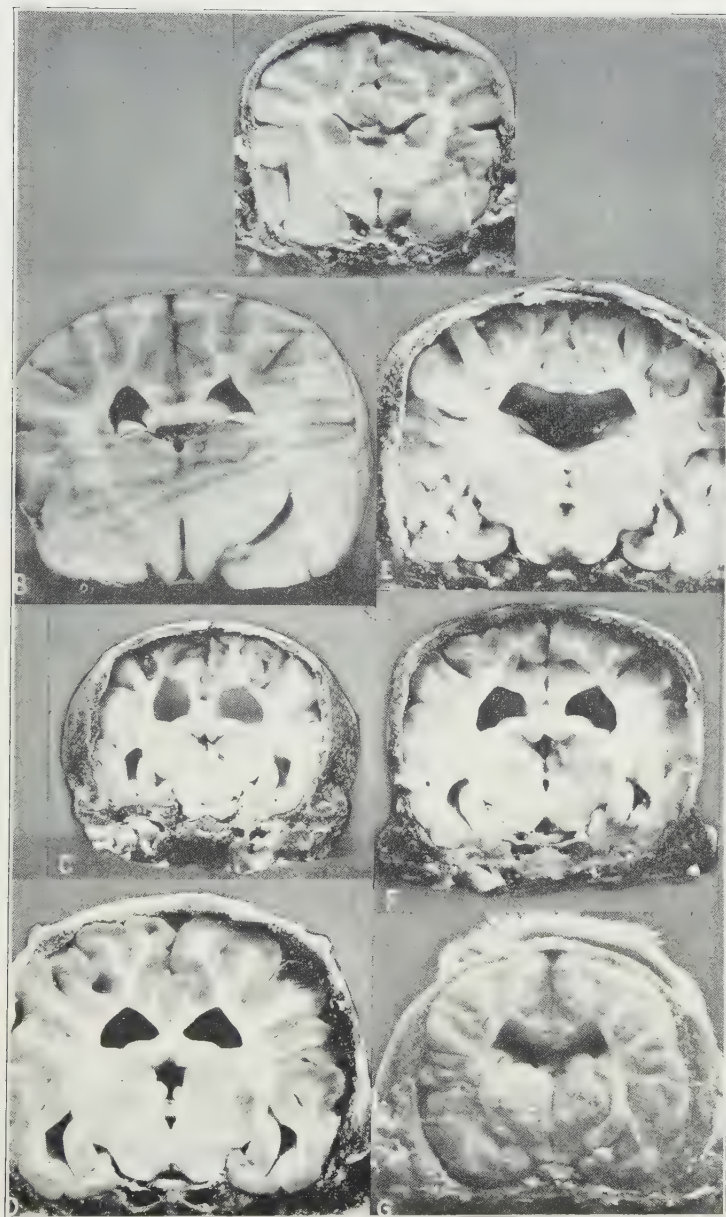


FIG. 74

record symptoms which varied from difference in behavior to severe convulsive seizures.

The clinical course in most of the adult dogs was short because of the brief intervals between the injections. Many of them died within a few days after their last injection with gradually increasing debility marked chiefly by emaciation and irritability. They were hypersensitive and would cry out if handled. One of the adult dogs was given four injections in the cisterna magna over a period of one month, and was kept under observation thirty days after the last injection. During this period of thirty days there was gradually increasing weakness and because of the very poor physical condition, it was sacrificed with chloroform.

The most striking clinical course was seen in the younger dogs. This was first noticed in the behavior of the injected animals as compared with the control. After recovery from the immediate effects of the injection, the pups were less active, so that the treated puppies could be picked out of the litter by the fact that they retired to a corner of the room showing little of the characteristic tendencies of such animals to play. When stirred to activity, they would lose interest much more quickly than the control.

In spite of the fact that the puppies ate well, they were generally smaller and markedly thinner. The difference in size between the control and an injected animal was seen in a pup which had five injections, three over the cerebral cortex and two at the base over a period of forty-two days. The first injection was given when the dog was ten days old. When sacrificed sixty-three days after the first and 21 days after the last injection, the general condition was fair. All the organs were normal except the brain which is seen in figure 74, C. The dilatation of the ventricles is very definite when compared with that of the control pup as seen in figure 74, A. Examination of the meninges showed chronic thickening over the base and cortex similar to that shown in figure 84. Another striking example was seen in dog 56 (see protocol, page 222) which when three months old weighed scarcely half as much as the control. This pup had general convulsive seizures almost two months after the last injection. Scattered areas of meningeal thickening were found in the examination of the brain and associated with the thickening there were areas of cortical scarring (fig. 86).

Convulsive seizures immediately followed the injection in five of

the ten adult dogs in which the blood was injected over the cerebral cortex, and in one of the four dogs in which blood was injected into the lateral ventricles. There were no convulsions immediately following the injections when young pups were used.

Four of the twenty-six injected puppies had convulsions after complete recovery from the immediate effects of the injection with no indication of the seizure until a few minutes before the attack. The first pup had a convulsion twenty-three days after the last injection, survived for thirty-six hours during which time there were a great many seizures. The second had its first convulsion forty-five days after the last injection; this seizure was followed by many others and he died during the same day. In the third pup the first seizure occurred eighty days after the last injection; from this it recovered promptly and remained fairly well for seventy-two days when without warning, there was a second series of convulsions in which the animal died. The fourth pup had single convulsions ninety-three and ninety-four days after the last injection; from these it recovered. It was kept under observation eighty-seven days during which time it had no convulsions but was aggressive and ill-tempered and was killed in a fight with another dog.

The seizures were all similar starting with fine twitchings of a muscle group, usually the face and then spreading over the entire body. The animal would soon lose consciousness and fall. The facial expression before loss of consciousness showed marked anxiety. Following the attack the animal was dull and stupid and remained so between the seizures when they occurred in series.

Protocols of pups in which convulsions occurred

<i>Date</i>	<i>Amount injected</i>	<i>Remarks</i>	<i>Lesions</i>
<i>Pup 46</i>			
April 23/26	1.0 cc. in cisterna magna.	Satisfactory recovery.	Meningeal thickening more
June 7		Severe general convulsions.	marked over cerebral cortex
June 9		Died.	where there is some scarring.
<i>Pup 50</i>			
April 26/26	1.0 cc. in ventricle.	Recovery.	Meningeal thickening over cortex, chiefly at sulci; none over base.
May 14	3.5 cc. over left cortex.	Recovery.	
May 17	2.5 cc. over right cortex.	Recovery.	

<i>Date</i>	<i>Amount injected</i>	<i>Remarks</i>	<i>Lesions</i>
June 9		Severe convulsive seizures. Died.	
<i>Pup 54</i>			
January 31/27	0.5 cc. in cisterna magna.	Respiratory embarrassment.	Meningeal thickening at base
February 11	0.8 cc. in cisterna magna.	Very limp for some minutes following injection.	and some areas of the cortex with cortical scarring.
May 2		Severe general convulsive seizures.	
July 13		Series of general convulsive seizures. Died.	
<i>Pup 56</i>			
February 2/27	0.5 cc. in cisterna magna.	Rapid recovery.	Brain not sectioned; in poor condition when received in the laboratory.
February 14	1.0 cc. in cisterna magna.	Rapid recovery.	
May 18		General convulsive seizure.	
May 19		General convulsive seizure. Died.	
August 15			

In addition to the four pups which developed convulsions, two were observed forty-three and twenty-nine days respectively after the last injection with severe twitchings involving all the muscles of the body without loss of consciousness. In one of these the twitchings continued throughout the day; the dog was greatly weakened and died during the night. In another, the dog previously well, had twitchings for three days, and on the morning of the third day was very weak, twitched constantly, and died before noon. On the lateral surface of the tongue there was a laceration which was perhaps due to biting during a general convulsive seizure in the night.

Protocols of the pups with general muscle twitching

<i>Date</i>	<i>Amount injected</i>	<i>Remarks</i>	<i>Lesions</i>
<i>Pup 59</i>			
February 28/27	0.8 cc. in cisterna magna.	Satisfactory recovery.	Moderate meningeal thickening at base.
March 9	0.5 cc. in cisterna magna.	Recovery.	

<i>Date</i>	<i>Amount injected</i>	<i>Remarks</i>	<i>Lesions</i>
March 28	1.0 cc. in cisterna magna.	Recovery.	
May 6		Weak and sick in appearance. Twitching.	
May 8		Weak with irregular twitching of all muscles, rhythmical twitching of the right hind leg. Head drawn to right.	
May 9		Irregular twitching of all muscles, rhythmical twitching of right foreleg. Died.	
<i>Pup 61</i>			
February 28/27	1.5 cc. in cisterna magna.		Very slight meningeal thickening at base.
March 28		Very poor shape. Twitching, unsteady, restless and listless.	
March 29		Died.	

Convulsions or muscle twitchings were not observed in six other pups which died from nine to sixty-three days after the injections.

Protocols of the pups which died without having had convulsions or muscle twitchings

<i>Date</i>	<i>Amount injected</i>	<i>Remarks</i>	<i>Lesions</i>
<i>Pup 32</i>			
March 26/26	3.0 cc. over right cortex.	Satisfactory recovery.	Meningeal thickening over cortex.
April 4		Died.	
<i>Pup 33</i>			
March 12/26	1.0 cc. over right cortex.	Satisfactory recovery.	Moderate degree of meningeal thickening over the right and left cortex.
March 26	2.5 cc. over right cortex.	Satisfactory recovery.	
April 4		Died.	
<i>Pup 34</i>			
March 12/26	1.0 cc. over right cortex.	Satisfactory recovery.	Meningeal thickening over cortex with some scarring.
March 26	3.0 cc. over right cortex.	Satisfactory recovery.	

<i>Date</i>	<i>Amount injected</i>	<i>Remarks</i>	<i>Lesions</i>
April 16	4.0 cc. over right cortex.	Satisfactory recovery.	
April 20	3.0 cc. over right cortex.	Satisfactory recovery.	
April 28	2.0 cc. over right cortex.	Satisfactory recovery.	
May 13		Died.	
<i>Pup 36</i>			
March 19/26	3.0 cc. over right cortex.	Satisfactory recovery.	No section; brain in poor condition when received in the laboratory.
March 29	3.0 cc. over right cortex.	Satisfactory recovery.	
April 16	4.0 cc. over right cortex.	Satisfactory recovery.	
April 20	3.0 cc. over right cortex.	Satisfactory recovery.	
April 28	2.5 cc. over right cortex.	Slow recovery.	
May 17		Died.	
<i>Pup 44</i>			
April 23/26	1.0 cc. in cisterna magna.	Satisfactory recovery.	No section; brain in poor condition when received in the laboratory.
June 9		Died.	
<i>Pup 70</i>			
March 28/27	1.25 cc. in cisterna magna.	Satisfactory recovery.	Moderate degree of meningeal thickening at base.
May 30		Died.	

In addition to the above twelve puppies which died as the result of the injection, eight injected pups and two controls were sacrificed when about half grown for histological study. Six of the injected pups are living and apparently well. More than one year has elapsed since the last injection of the six living puppies. At this time these animals show no ill effects resulting from the injection. They will be sacrificed for histological purposes when full grown. Of the five controls two which were sacrificed for histological study seemed entirely normal at the time of the sacrifice and the three remaining control dogs are living and well.

LESIONS

The study of the brains of the animals which died a short time after the last injection showed grossly, blood staining of the portion of the meninges with which blood had come in contact, and thickening of the stained membrane. In the brains removed long after the last injection, the gross appearance varied from slight thickening of the meninges to normal. Frontal sections through the fore-brain ventricles showed a degree of dilatation of the ventricles varying from slight to well marked. In the adult dogs ventricular dilatation was less frequent than in the case of the pups. Of the seven adult dogs in which one or more injections were given over the cortex, and in seven adult dogs which had one or more injections in the cisterna magna only one showed a well marked degree of dilatation of the ventricles. A photograph of the frontal section of the brain of this dog is shown in Fig. 74, B. This animal had six injections of blood in the cisterna magna over a period of thirty-nine days and was sacrificed two days after the last injection.

Six of the nineteen puppies injected on which autopsies have been done had definite dilatation of the ventricles. Photographs were made of five of these pups and are shown in figure 74. As shown by the protocols, all of the puppies with dilated ventricles had one or more injections in the cisterna magna, in addition some were injected over the cortex. Two received but one injection, one 2 cc. and the other 1.25 cc. of blood in the cisterna magna. One of these was sacrificed twenty-one days after the last injection and the other was found dead in the cage sixty-two days after the injection. The dilatation of the ventricles was always associated with meningeal thickening. Clinically, these animals gave no evidence of the dilatation.

<i>Dog</i>	<i>Date</i>	<i>Protocols of pups with dilatation of the ventricles</i>		<i>Lesions</i>
		<i>Amount injected</i>	<i>Remarks</i>	
January 23/25		1.0 cc. in cisterna magna.	Satisfactory recovery.	Marked meningeal thickening of meninges at base and in some areas of cortex.
February 4		1.5 cc. in cisterna magna.	General convulsion.	
February 9		1.5 cc. in cisterna magna.	Slow recovery.	
February 18		1.5 cc. in cisterna magna.	Satisfactory recovery.	
March 1		2.0 cc. in cisterna magna.	[Slow recovery.	

<i>Date</i>	<i>Amount injected</i>	<i>Remarks</i>	<i>Lesions</i>
March 3	1.0 cc. in cisterna magna.	Slow recovery.	
March 5		Sacrificed.	
<i>Pup 31</i>			
March 12/26	1.5 cc. over right cortex.	Satisfactory recovery.	Marked meningeal thickening over base and cortex.
March 29	2.5 cc. over right cortex.	Satisfactory recovery.	
April 12	2.0 cc. in cisterna magna	Satisfactory recovery.	
April 20		Sacrificed.	
<i>Pup 35</i>			
March 17/26	3.0 cc. over right cortex.	Satisfactory recovery.	Moderate meningeal thickening at base, not much over cortex.
March 24	0.5 cc. over right cortex.	Slow recovery.	
March 29	2.5 cc. over right cortex.	Satisfactory recovery.	
April 16	1.0 cc. in cisterna magna.	Satisfactory recovery.	
April 28	2.5 cc. in cisterna magna.	Satisfactory recovery.	
May 10		Sacrificed.	
<i>Pup 37</i>			
March 17/26	3.0 cc. over right cortex.	Satisfactory recovery.	Marked meningeal thickening at base and moderate over cortex, especially at sulci.
March 26	3.0 cc. over right cortex.	Satisfactory recovery.	
April 12	1.0 cc. in cisterna magna.	Satisfactory recovery.	
April 28	1.5 cc. in cisterna magna.	Satisfactory recovery.	
May 5		Sacrificed.	
<i>Pup 45</i>			
April 23/26	2.0 cc. in cisterna magna.	Satisfactory recovery.	Very slight meningeal reaction over base.
May 14		Sacrificed.	
<i>Pup 47</i>			
April 23/26	1.0 cc. in cisterna magna.	Satisfactory recovery.	Moderate degree of meningeal thickening at base.
April 30	2.0 cc. in cisterna magna.	Satisfactory recovery.	

<i>Date</i>	<i>Amount injected</i>	<i>Remarks</i>	<i>Lesions</i>
May 10		Sacrificed.	
<i>Pup 70</i>			
March 28/27	1.25 cc. in cisterna magna.	Satisfactory recovery.	Moderate degree of meningeal thickening at base.
March 29		Died.	

The microscopic study of the brains showed meningeal thickening where blood came in contact with the membranes. In the acute stage, that is in the dogs sacrificed soon after the last injection, the meninges showed marked cell proliferation. In figure 75 the thickened membrane is shown at the base of the brain of a dog which had four injections in the cisterna magna over a period of seventeen days and was sacrificed two days after the last injection. After the acute reaction passed off, there was a deposit of fibrous tissue with pigment-laden phagocytes as seen in figure 76 which is a photograph of a section of the meninges taken from the base of a dog which had four injections over a period of thirty-one days. Following the last injection the animal's general condition grew progressively worse and it was sacrificed thirty days after the last injection.

This condition is not limited to the base as shown in figure 77 taken from the same dog over the crest of the gyrus adjacent to the longitudinal sinus. The meningeal thickening is often very marked at the site of sulci diminishing as the crest of the sulcus is reached. In figure 78 taken from dog 10, see protocol, page 225, the meningeal thickening at a sulcus is seen. The heavily stained cells are phagocytes filled with blood pigment. The pigment loaded cells are found even in the chronic state of the meningeal thickening secondary to the injection of blood and are useful in the microscopic examination of the specimens as is blood-staining in the gross appearance in determining the areas of meninges with which the blood had come in contact.

In figure 78 at *a* two pigment filled phagocytes are seen in a perivascular space well below the surface of the cortex indicating an early stage of cortical alteration. This cortical alteration is frequently secondary to a condition seen in figure 79, where the meningeal reaction has progressed to a point of matting together of the membranes in a sulcus entirely obliterating the normal meningeal spaces. With a beginning cortical alteration as seen in figure 78 active cell proliferation (fig. 80) ensues which progresses for a time resulting in fibrous tissue deposit constituting a scar as shown in figure 81.



FIG. 75. A section taken from the base of an adult dog which received four injections of blood from 1 to 1.5 cc. in amount in the cisterna magna over a period of seventeen days. The animal was sacrificed two days after the last injection. The meninges were thickened and the seat of active cell proliferation.

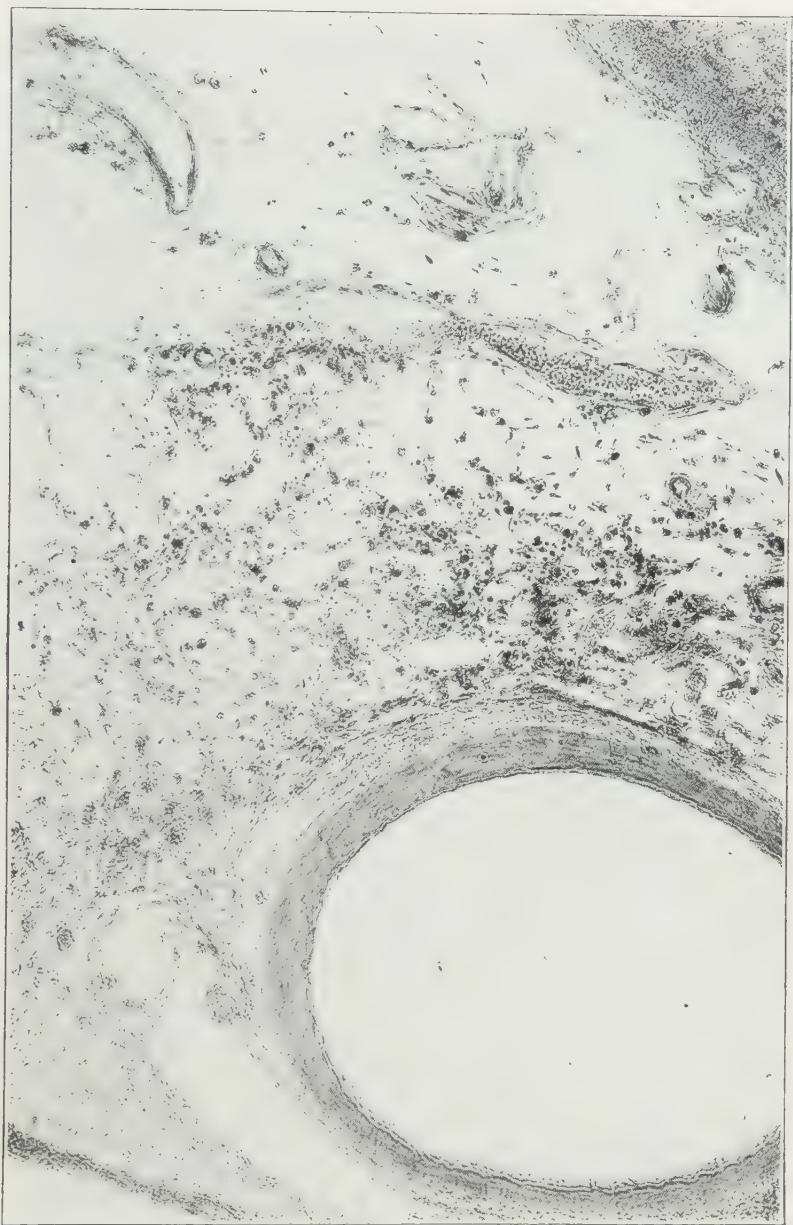


FIG. 76. A section taken from the base of an adult dog which had four injections in the cisterna magna over a period of thirty-one days; animal was sacrificed thirty days after the last injection. In comparison with figure 75 there is a diminution of cells but an increase of fibrous tissue. The fibrous tissue mesh contains a number of pigment loaded phagocytes.

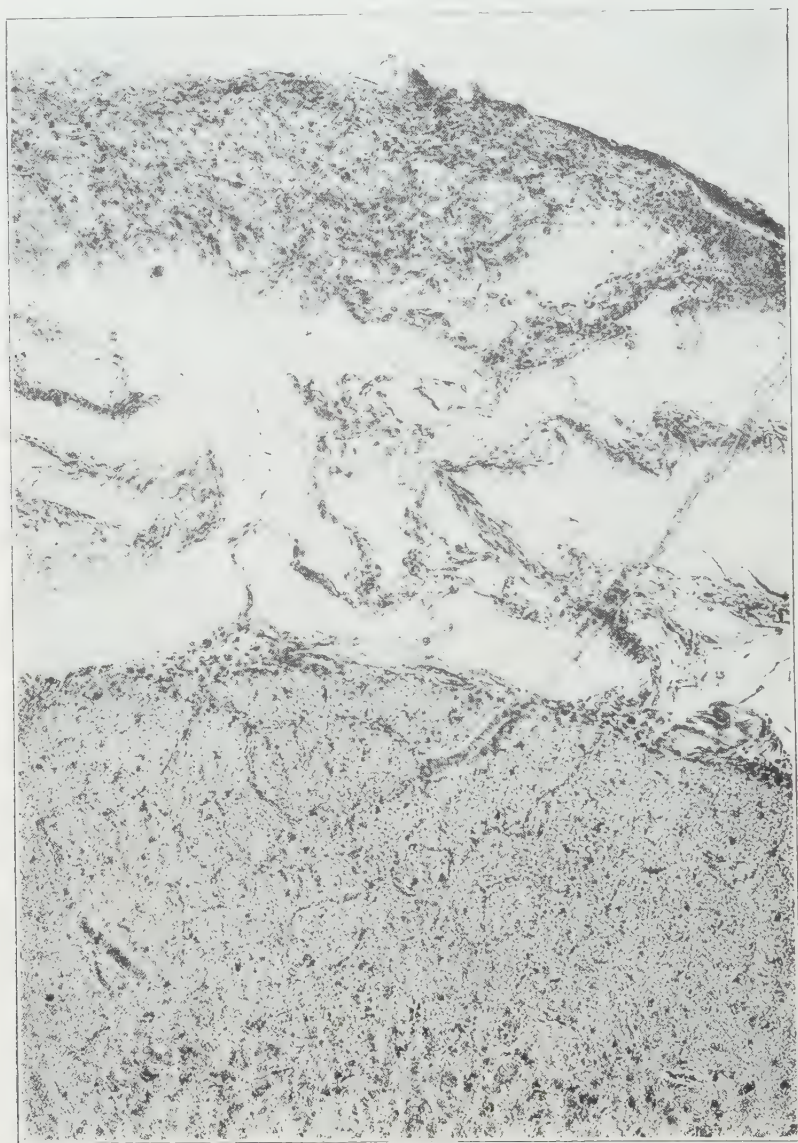


FIG. 77. A section taken from the crest of a gyrus adjacent to the longitudinal sinus of the same dog as figure 76 showing an increase of fibrous tissue elements.

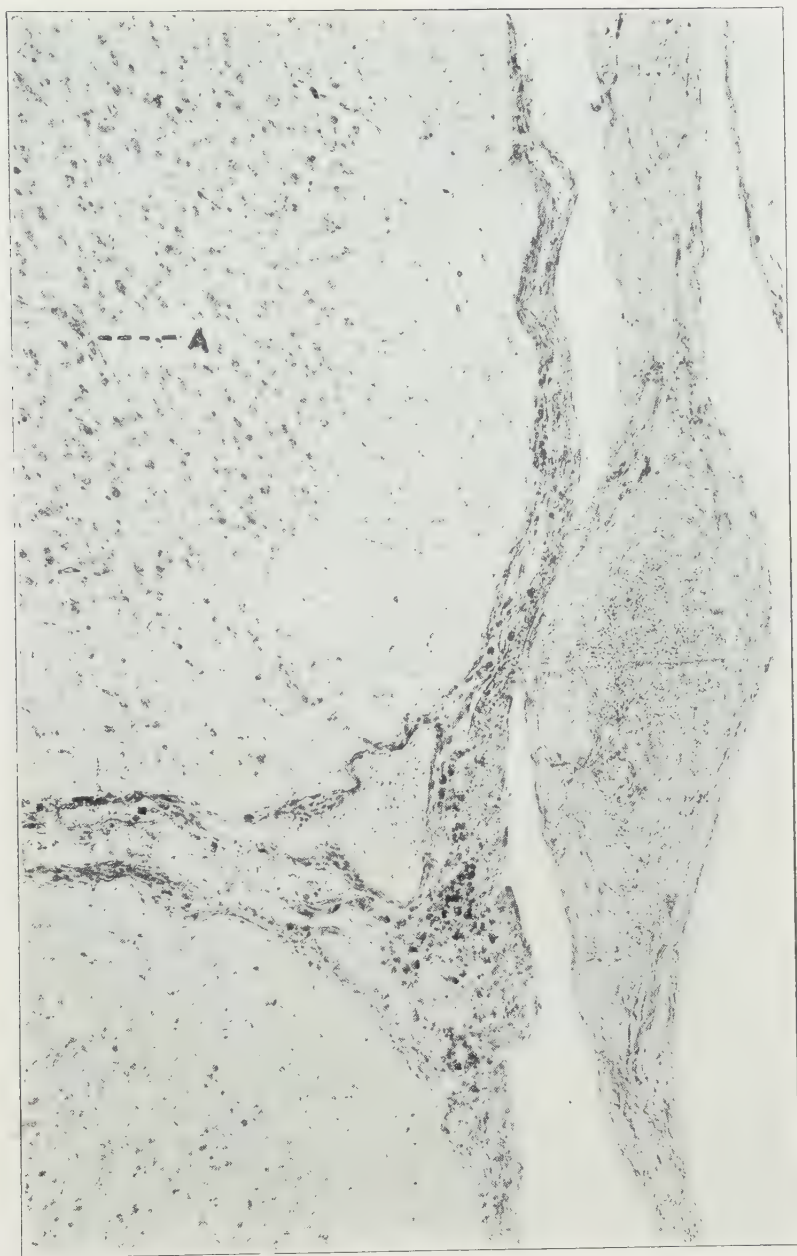


FIG. 78. A section from the mesial wall of the hemisphere adjacent to the falx showing meningeal thickening at the top of a sulcus. The dark cells are phagocytes filled with blood pigment. At *a* two pigment filled phagocytes are seen in the perivascular space.

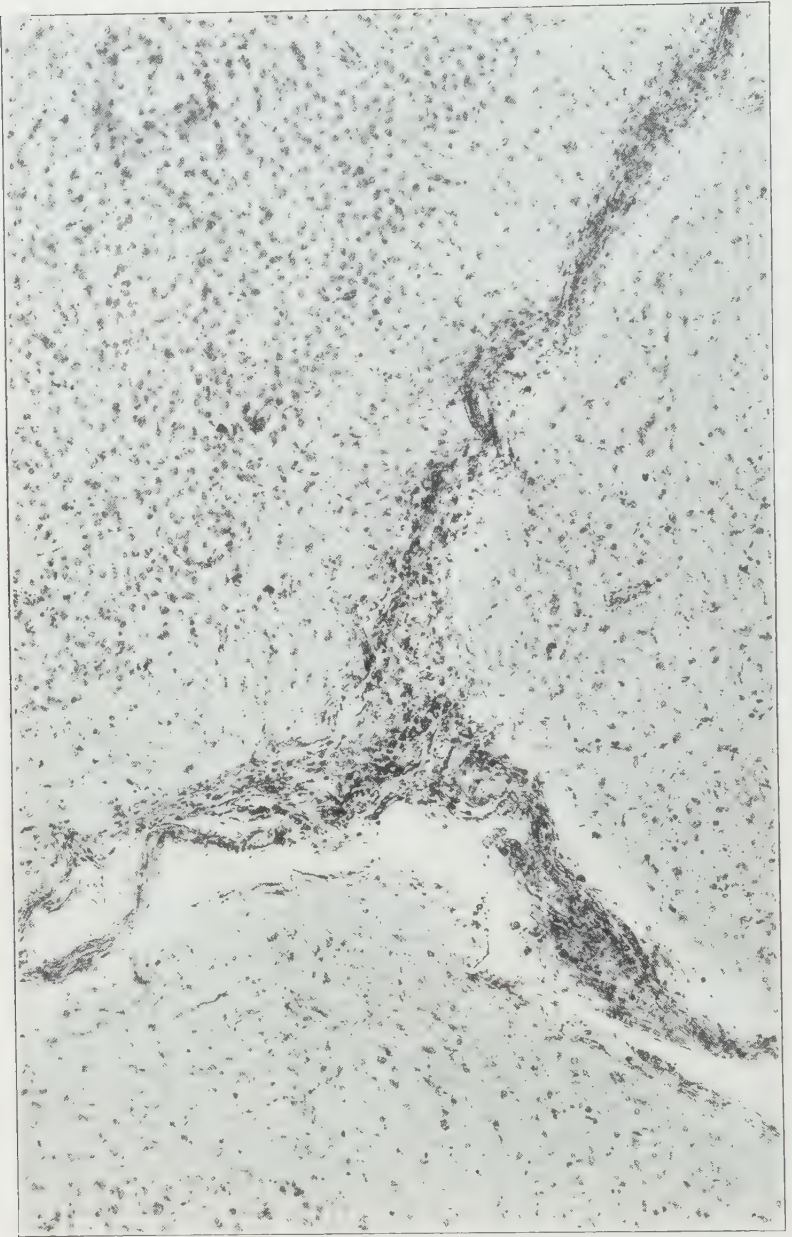


FIG. 79. A section taken from dog 10 showing the matting together of the meninges which is the forerunner of cortical alterations.

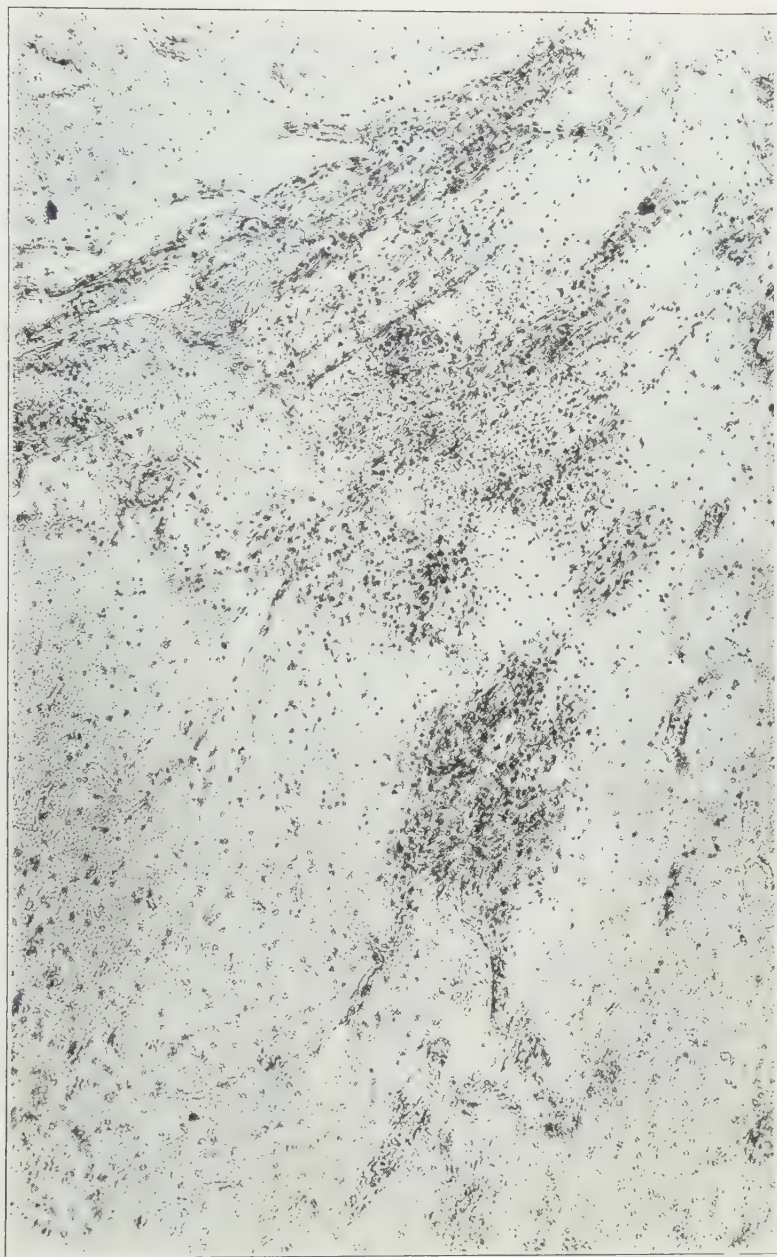


FIG. 80. A section of cortex adjacent to a sulcus in which there is matting of the meninges. Active cell proliferation within the cortex is shown.



FIG. 81. A further stage of cortical scarring following the cell proliferation as shown in figure 80.

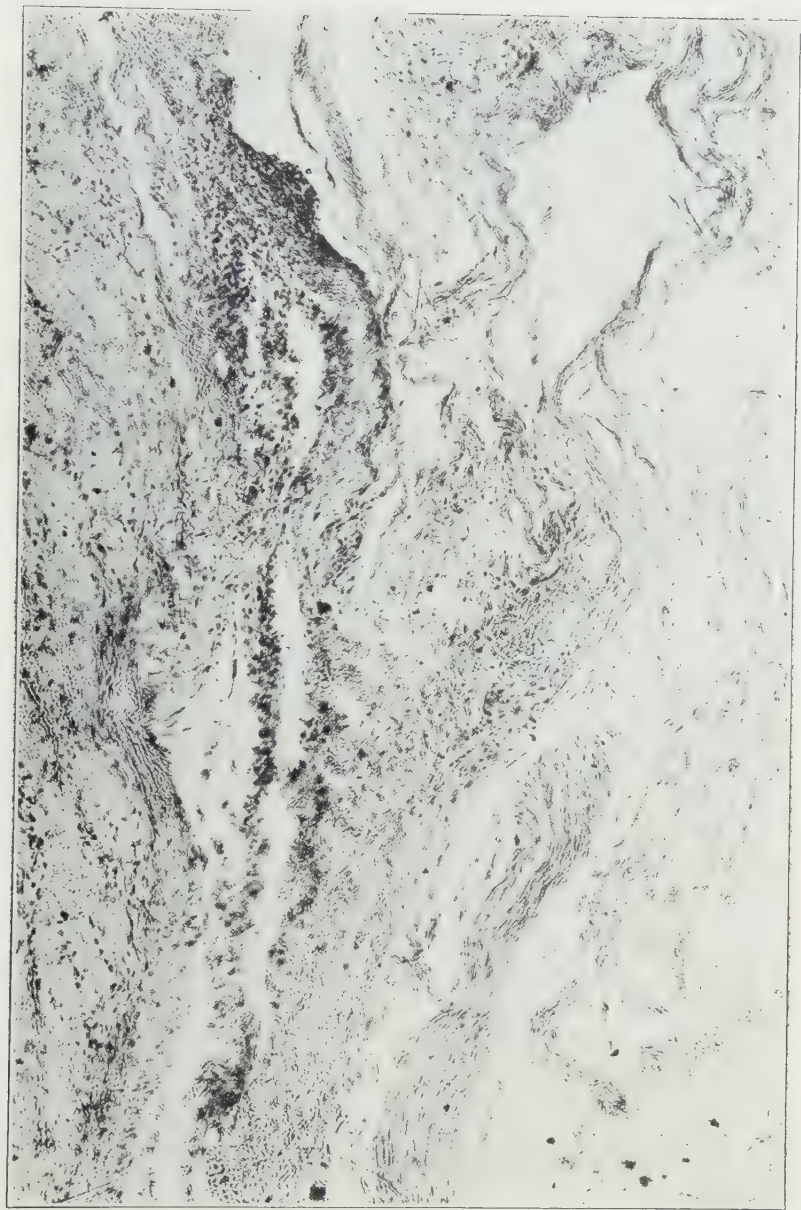


FIG. 82. Active cell proliferation in the meninges covering the optic nerve. The section was taken from dog 10.



FIG. 83. A section taken from the optic nerve of one of the control pups showing the normal meningeal coverings of the nerve.

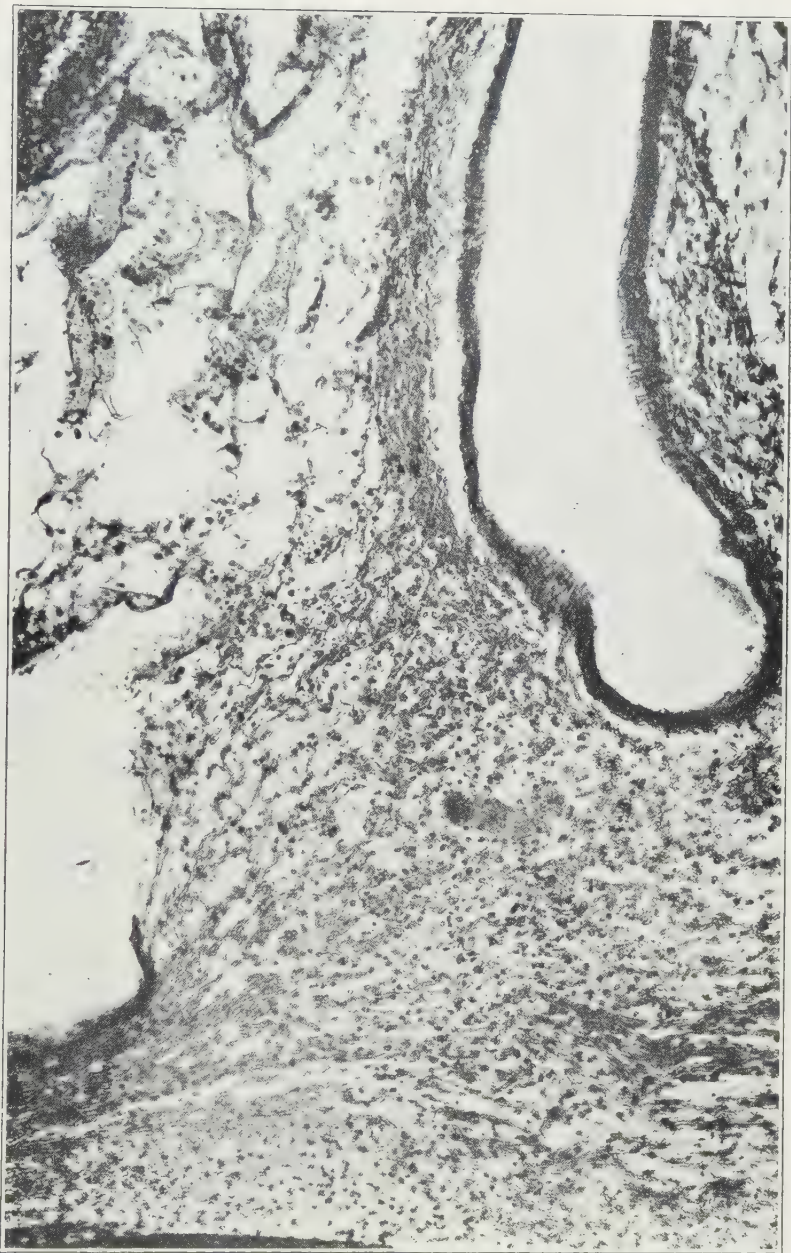


FIG. 84. A section from the base of the brain of pup 46 which died following convulsive seizures forty-seven days after an injection of 1 cc. of blood in the cisterna magna. There is marked meningeal thickening with cell infiltration.

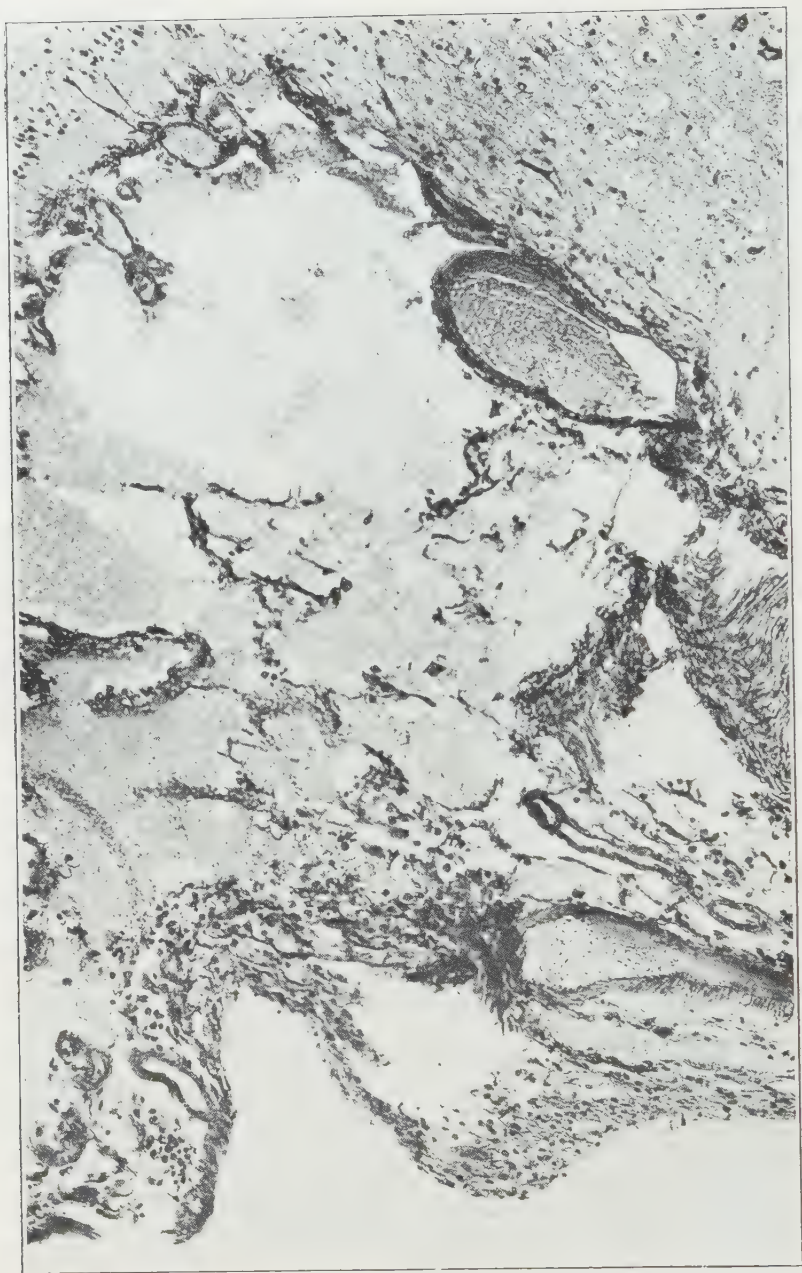


FIG. 85. A section of the meninges from the base of pup 59 which died during convulsions forty-two days after receiving three injections of blood in the cisterna magna, showing an increase of fibrous tissue elements.

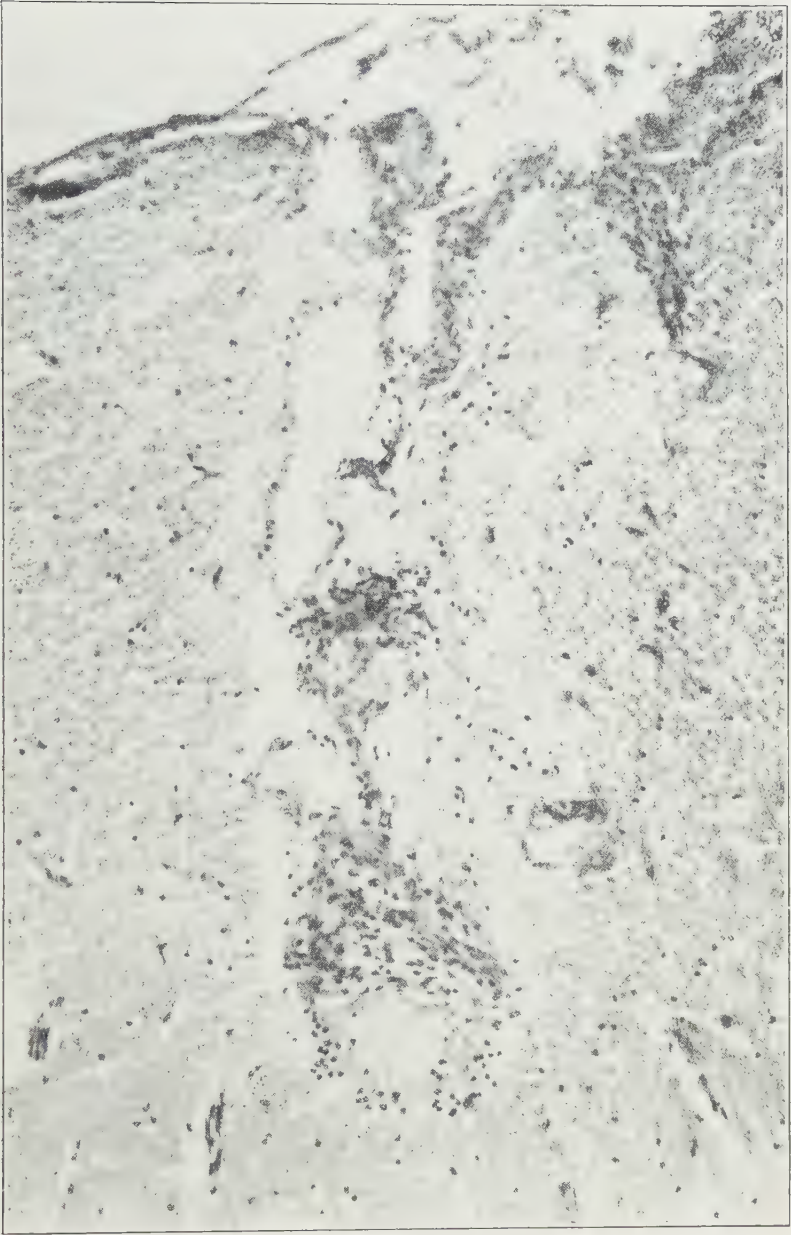


FIG. 86. A section taken from the occipital pole of pup 54, showing meningeal thickening in a sulcus with beginning cortical alteration.

The meningeal reaction extends to the membranes covering the optic nerve, as shown in figure 82, a photograph of a section of the optic nerve and its coverings taken from dog 10 as compared with the same structures in figure 83, taken from one of the control puppies.

In the pups which presented symptoms and those that died, meningeal thickening as shown in the previous sections was observed. For example, figure 84 taken from the base of the brain of pup 46, see protocol, page 221, the meninges are thickened and contain a large amount of fibrous tissue. A photograph (fig. 86) taken from the occipital pole of the brain of pup 54 shows the meninges of a sulcus in active cell proliferation extending into the cortex at the site of a blood vessel.

CONCLUSIONS

Blood mixed with the cerebrospinal fluid of young and adult dogs produces neurological disturbance varying from slight difference in behavior to severe convulsive seizures. Though some of the animals were severely affected by small quantities of blood mixed with the cerebrospinal fluid, others have survived more than a year, and are apparently normal.

Following the introduction of blood in the cerebrospinal fluid there begins a reaction of the parts of the meninges which have come in contact with the blood. The meningeal reaction tends to subside and may disappear as the blood disappears from the fluid. After several weeks the cell elements are less numerous in the meninges but a large amount of fibrous tissue is present.

Late in the course of the meningeal reaction changes in the structure of the cortex are observed.

Moderate dilatation of the ventricle occurs not infrequently following the introduction of blood into the cerebrospinal fluid of young pups. The condition may occur in adult dogs but with less frequency.

These facts as applied to patients with bloody cerebrospinal fluid are discussed in another paper in which twenty-seven representative cases are included.²

Grateful acknowledgement is tendered to Dr. Adolf Meyer under whose direction the work has been carried on. I wish to thank Dr. Frank Ford for his assistance in some of the experiments and Miss

² "Clinical Data Relative to Bloody Cerebrospinal Fluid" to appear in a later issue of *Archives of Surgery*.

Cecilia Bisson for valuable assistance in the making of motion picture films, for the study of the behavior of the animals, and for the illustrations of the paper.

DISCUSSION

The following questions submitted to Dr. Bagley before the Commission, together with the answers to them, are here reported verbatim.

DR. COBB: Are not the extravasations of blood deep in the cortex and the scars found in the cortex due to hyperemia during convulsions rather than to injection of blood into the subarachnoid space?

DR. BAGLEY: The section showing cortical scarring is from the brain of a dog that had convulsions immediately following the injections but had no seizures during the later course. I do not believe it is due to the hyperemia caused by the convulsions. The process of scarring is a slow one, started by the injected blood in the perivascular space and can be traced from the early stage marked by pigment loaded phagocytes in the perivascular space (fig. 79) to cell proliferation (fig. 80) and fibrous tissue deposit (fig. 81).

DR. O. J. RAEDER: Does Dr. Bagley feel that the pigment laden leukocytes about scars of the brain might result from hemorrhages due to convulsions instead of the injected blood traveling into the brain.

DR. BAGLEY: If I understand your question, it is, could the blood be due to the convulsion and the phagocytes loaded with pigment from that blood? I think not. I should not expect blood in the cerebrospinal fluid as a result of a convulsive seizure. The course of the injected blood could be followed by the staining of the meninges in the cases autopsied early and by the pigment loaded phagocytes in the late autopsies in the same way that we traced ink granules in one of the dogs injected with India ink.

DR. W. A. WOLFF: Were there any changes in the chorioid plexus?

DR. BAGLEY: We have not studied the chorioid plexus.

DR. C. S. DANZER: What part did anaphylactic phenomena play in the convulsions? Did convulsions ever result after only one injection?

DR. BAGLEY: Yes, pup 46 had but one injection of 1 cc. in the cisterna magna.

DR. TAYLOR: Was the dog's own blood used in each case?

DR. BAGLEY: Yes, we used the dog's own blood, taken from the leg vein in the adult dog and the longitudinal sinus in the younger dogs.

DR. ELSBERG: The first part of Dr. Danzer's question was, What part did anaphylactic phenomena play in the convulsions?

DR. BAGLEY: I do not know. I should like to know whether any one feels it plays a part.

DR. TAYLOR: Are the convulsions more readily produced depending upon where the injections are made?

DR. BAGLEY: Such factors as quantity of blood or too much pressure on the syringe were variable and perhaps responsible for the early seizures. We, therefore, attached less importance to the immediate convulsions.

Three of the pups, (nos. 46, 54, 56) which had late convulsions had cisternal injections only and the fourth pup (no. 50) in this group had one injection in the ventricle and two in the subarachnoid space over the cerebral cortex. The two pups (nos. 59, 61) which died of general twitching had cisternal injections only.

DR. TIMME: Dr. Bagley, are your conclusions at all applicable to the extravasation of blood during the intracranial operation in humans?

DR. BAGLEY: I think the story hangs on that. Dr. Grant was good enough to come down to Baltimore and look over this work with me during the year, and he spoke about that, but the whole story is changed when you open the dura. There is a difference between the blood in a postoperative case and one in which the blood is in a more or less sealed box. After operations there is drainage through the open dura. Traumatic cases requiring operations improve because of the opening in the dura which permits free drainage of bloody cerebrospinal fluid. The variation in the amount of drainage is dependent, in part at least, upon the necessity of external drainage.

DR. BARKER: I should like to ask Dr. Bagley whether he has tried, or thought of trying, corpuscles alone, or pure hemoglobin alone, or serum alone, to produce the same reactions?

DR. BAGLEY: The only thing we did in addition to what I have reported was to inject some citrated blood in one pup.

What I am anxious to do now is to try blood pigment. I rather think from the way the phagocytes loaded themselves up with blood pigment, they would perhaps do the same thing without the rest of the blood, but I would not state that as a fact. We are keeping the other pups with the hope of following them as full grown dogs and expect to go on with the work, but we felt that we had gone far enough to make this report.

DR. KENNEDY: Is it not remarkable that severe injuries to the skull and brain are not more often followed by convulsive seizures? In view of the constancy of convulsions following your experiments, is it not remarkable that in the human animal convulsions are not the rule following a gunshot injury of the brain or gross trauma?

DR. BAGLEY: I think that most of us fear convulsive seizures after a severe laceration of the brain. I know in the cleanup of the soldiers we had a tremendous amount of epilepsy, and I might say that this work is not intended to cover traumatic epilepsy as a whole. It is only the epilepsy that occurs where there is a mixture of blood and cerebrospinal fluid.

Just as soon as you talk about depressed fractures of the skull, extensive lacerations of the brain substance, and large clots over the cortex, you are getting out into a different grouping.

DR. KENNEDY: Of 23,000 head injuries, there were only 14 per cent with convulsions of late development. After the inception of the injury, the number was 10 per cent. That is not "tremendous."

DR. BAGLEY: I think here again just as soon as you get a severe traumatism with rupture of the dura or break of the cortex or severe injury that requires an operation you open up the dural space just as you do in the instance of Dr. Timme's postoperative case, and then you are out of this group entirely. I am talking about blood that is free in the cerebrospinal fluid in a tightly closed cranial box. If that patient is operated upon the dura is opened, then I think he takes care of this blood through that dural opening, and it brings you back to the question of what you ought to do in the slightly injured cases. If a man comes in with severe gunshot injury, with an extensive depressed fracture of the skull, with brain substance hanging out, the dura open, there is not much question about that patient. The type of case we are discussing in this particular group is the one with what seems like a slight injury which goes on and develops various complications later, anything from backwardness in a child to severe epilepsy.

DR. KENNEDY: Then the result of your observations would be that any case injured and showing bloody cerebrospinal fluid ought to be decompressed?

DR. BAGLEY: Oh, no.

DR. DAVIDOFF: Would Dr. Bagley suggest, in view of this experience, that decompression should be done with opening of the dura in every traumatic case that shows bloody fluid?

DR. KENNEDY: That is exactly my question.

DR. BAGLEY: I would answer no. From the standpoint of the surgeon it is very nice to be able to say to the physician that you do not need to send all of these cases to the surgeon. Anybody can do a lumbar puncture, and there are groups of cases, new born, children, and adults that can be better cared for by lumbar puncture than by decompression.

Whether you make the diagnosis of a hemorrhage into a subarachnoid space or not, a puncture should be done, preferably long enough after the injury to allow the fluid to be yellow instead of fresh so that you obviate the question of blood due to your puncture. If the fluid is perfectly clear and the patient is having symp-

toms, it should be considered as not due to that and a record made of it so that you know in the future. On the other hand, if there is the slightest yellow tinging of the cerebrospinal fluid, I think that a lumbar puncture should be done until the fluid is entirely clear and until all symptoms have disappeared.

In the case of infants with small hemorrhages untreated in the first weeks, rigidity, especially of the post cervical muscles, may be the only disturbance. The cerebrospinal fluid shows no trace of the early hemorrhage but the rigidity subsides after repeated lumbar punctures.

In some cases you will not be able to get the fluid entirely clear in this way and the symptoms may persist, then a more radical operation must be done. The cases must be picked out and treated by lumbar puncture, decompression or bone flap.

CHAPTER XVII

THE DETERMINATION OF THE SYSTOLIC AND DIASTOLIC PRESSURE IN THE CENTRAL ARTERY OF THE RETINA (METHOD OF MAGITOT)

ITS VALUE IN THE EARLY RECOGNITION OF INCREASED INTRA-
CRANIAL PRESSURE

CYRIL BARNERT, M.D.

A METHOD of determining increased intracranial pressure, entirely independent of any of the usual objective and subjective means now employed, is obviously useful and desirable. Such a method is available and has been employed abroad but not as generally as its value deserves. It depends upon the fact that an increase in intracranial pressure produces elevation of the blood pressure in the cranial arterial system, including the retinal arteries. The pressure in the retinal arteries can be measured and by comparison of these measurements with those of the general arterial pressure, one finds in increased intracranial pressure a fairly constant and measurable variation from the normal ratio.

The method of measuring the pressure in the retinal arteries developed by Baillart in 1917 and further elaborated and improved by Magitot in 1919, is based upon the following physiological facts.

Normally there is no visible pulsation in the retinal arteries because the minimal pressure therein is higher than the intra-ocular pressure. If the intra-ocular pressure be increased to the point when it equalizes the pressure within the vessel wall or if the arterial pressure become decreased to the level of the intra-ocular pressure, definite rhythmic pulsations of the arteries will become visible. A "spontaneous pulse" is commonly seen in morbid states, as in glaucoma, aortic insufficiency, syncope and severe anemias. Visible retinal pulsation can also be produced and readily observed by the simple expedient of making digital pressure on the globe while observing the fundus with an oph-

thalamoscope, and the amount of pressure necessary to establish this pulse, due allowance being made for the intra-ocular pressure existing at the time, can be accurately determined and expressed in degrees of mercury. If the pulsation in the artery having been established by externally applied pressure, further pressure be applied to the globe, a point will be reached when this pressure is sufficient to empty completely the retinal arteries, thereby abolishing the pulsation and permitting the determination of the systolic pressure.¹

The measurement of the amount of pressure necessary to establish

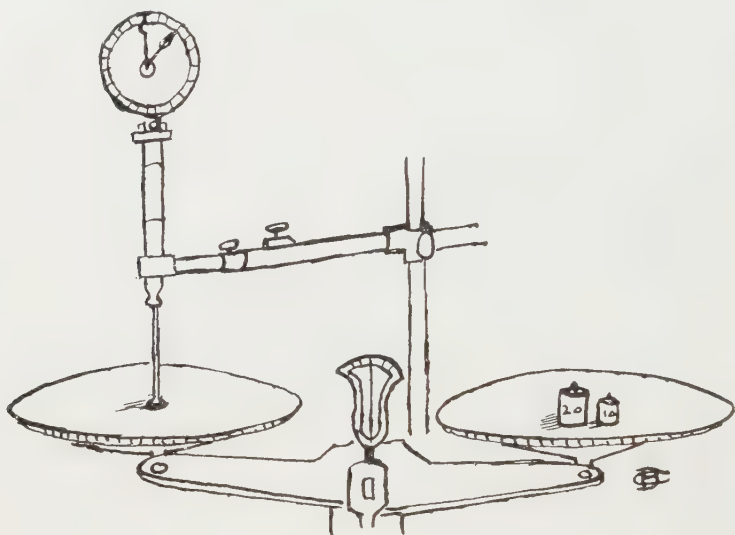


FIG. 87. Simple method of testing the accuracy of the dynamometer (after Bailliart and Magitot).

¹ An interesting physiological side light is here worth noting. At the moment when the arteries are completely emptied, the eye becomes totally blind showing the absolute dependence of the retina upon its blood supply. The simple experiment of closing one eye, gazing at a light with the other and applying digital pressure to the open eye through the upper lid, will prove this. Restoration of vision is complete the moment the pressure is released.

Halle claims that the retina cannot withstand more than eleven minutes absence of blood supply without permanent damage but recently in sudden complete blindness in one eye from extensive hemorrhage into the orbit during the course of an intranasal operation, we were able by a rapid drainage of the orbit through an external incision to restore vision after eighteen minutes of anemia.

and then to obliterate the retinal pulse is accomplished by the use of Bailliar's dynamometer or pressure gauge and is based upon the tension of a spring. It consists of a small cylindrical barrel from one end of which protrudes a piston with a button-like terminal. Vertical pressure upon this button increases the tension of the spring in the cylinder and the amount of pressure is noted on a small scale in grammes of water, engraved on the face of a dial and reading from 0 to 150 grams. An ingenious double needle on the dial permits the actual reading to be made without holding the dynamometer in action, thus permitting the combined ophthalmoscopy and dynamometry to be done by one observer.

The button end of the instrument, which is applied to the eye is somewhat convex and smooth and can be applied to the globe without danger even if badly applied or if it override the cornea.

TECHNIQUE

As it is essential first to determine the tension of the globe by tonometry, it is necessary to instill one or two drops of cocaine in the conjunctival sac. The mydriatic action of this drug also facilitates the fundus examination though this can be done through an undilated pupil. We prefer the Schiotz tonometer, taking the tension of each eye with the patient lying down. The tension in each eye is noted for reference later. The next step is the determination of the amount of pressure on the globe necessary to induce the appearance of the retinal pulse. This is accomplished by applying the button end of the dynamometer to the ocular conjunctiva just behind the insertion of the external rectus tendon. The instrument is held horizontally to eliminate the weight of the instrument. The instrument is held lightly between the thumb and the index finger, the other fingers resting upon the patient's brow. The other hand of the observer, armed with a luminous ophthalmoscope is approached to the eye and focused upon an artery on the optic disc. This is essential; it will not suffice to select a vessel in the retina away from the disc, or a vein upon the disc. The observer applies gradually increasing pressure upon the globe with the dynamometer, keeping close watch upon the artery for the first evidence of pulsation. As in taking the general blood pressure, the first irregular oscillations are disregarded and the dial reading is made at the commencement of rhythmic pulsations. The dynamometer is then removed and the indicator scale is read and

noted. To determine the point of disappearance of the pulse the dynamometer is reapplied in the same way, an artery on the disc brought into view by the ophthalmoscope and increasing pressure applied to the globe until the artery pulse is not only established but completely arrested by the entire emptying of the vessel. The amount of pressure necessary to accomplish this is noted on the dial.

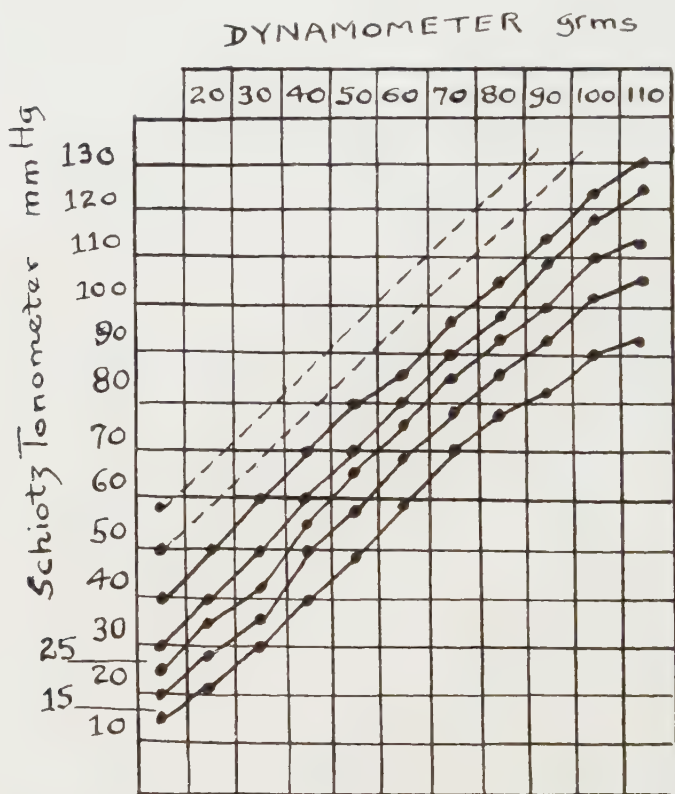


FIG. 88. Chart for translating dynamometric pressure figures from grams to mm. Hg (after Bailliart and Magitot).

For the purpose of accuracy, this procedure is repeated three successive times and the average of the three readings is considered the point in millimeters of water at which retinal pulsation is established and obliterated. The instrument, of course, is reset before each procedure simply by pushing the indicating arrow back to zero.

It must be remembered that these figures are not those of the total pressure upon the artery inasmuch as the intra-ocular pressure at the moment of the reading must be known and taken into account. Bailliart and Magitot, by a series of experiments upon the eyes of animals, have worked out a schedule whereby the initial tension of the globe being known, the proper factor representing the increased intra-ocular tension at any given point of externally applied pressure may be computed. This schedule is plotted in curves on a chart which permits the observer with the two readings, *i.e.*, the tonometric and the dynamometric, to convert into millimeters of mercury the figure noted on the dynamometer.

For example, if the eye before the use of the dynamometer showed an intra-ocular tension of 20 mm. Hg. and arterial pulsation was established at 30 grams and obliterated at 70 grams, we seek on the chart the intersection of the 20 mm. Hg. curve and dynamometric findings above at 30 and 70 respectively; now read the level of these intersecting points in the millimeters of Hg. scale and we find 35 mm. Hg. and 75 mm. Hg. These represent the diastolic and systolic pressures in the retinal artery.

So much for the actual mechanical technique. Now for its value. Without going into the complicated physiological questions which naturally arise, and which we leave to more experienced hands to clarify, we shall attempt to report the practical value, if any, of this procedure. Starting solely with the idea of familiarizing ourselves with the use of the instrument and checking the findings of Bailliart and Magitot, we met with one source of error after another until we were ready to give up the experiment in disgust. Gradually, however, we began to see daylight. By care in the many apparently unimportant steps in the procedure our technique commenced to become standardized and we became impressed with the tendency to uniformity of our readings. While we are not prepared, with our present experience and data, to assert a complete agreement with the published claims of the originators of this method, we are tremendously intrigued by the results so far obtained and we believe that with further care in all the minutiae of technique we shall probably be able to endorse many of the statements of Bailliart and Magitot.

We do not wish to give the impression that the difficulties of the procedure are such as to discourage its general use. There are many more difficult examinations which as ophthalmologists we are

trained to employ daily, and while we are not as optimistic as Magitot who "boldly affirms" that "a practitioner who knows how to use his ophthalmoscope will not take more than ten days to acquire the necessary skill" we insist that time, care and experience will make any one able to obtain uniform readings. As a matter of fact we frequently found more difficulty in determining the intra-ocular tension with the tonometer, especially in children and in poorly co-operating adults, than with the dynamometer. Nor, for practical purposes need one's results be absolutely accurate, for when a man has trained himself with due regard to the pitfalls of possible error to a point where his technique becomes standardized and uniform, his results will have a definite value even if another equally well trained observer obtains slightly different figures. There is ample leeway in determining one's final deductions, for instance for a comparison of the retinal blood pressure with the general blood pressure, to disregard the element of possible error in the determination of the retinal pressure. Just as the well established test of taking the blood pressure with the sphygmomanometer gives varying results in the hands of trained observers examining the same patient simultaneously, so the personal equation enters into the determination of the retinal pressure. If, to put it more plainly, one's technique, including errors, is uniform the results will be uniform and of value.

The more important factors in the mastering of the technique may be grouped as follows:

1. *Obtaining the dynamometer.* This instrument is not obtainable in America at present. It may be obtained from Giroux, 116, Rue du Temple, Paris, or from Boulitte, 16, Rue Babillot, Paris. The former makes only the simple pressure gauge, the latter both the simple gauge and the gauge with dial. The dial gauge (le modele a cadron) is preferable and costs about \$25 to import.

2. *Care of the instrument.* The accuracy of the instrument must be frequently checked by the use of a pair of scales. The instrument is firmly clamped with the button end in contact with one scale, and the figures on the dial verified by adding gram weights to the other scale. It must be handled with the care that an instrument of precision deserves and it must be kept clean and covered when not in use. The button end which comes in contact with the globe may be sterilized by boiling or by disinfectants, of which alcohol is perhaps the best.

3. *Tonometry.* The chart for determining the final result in millimeters of Hg. is based on readings made with the Schiøtz tonometer and this instrument should be used. It is obvious that the tonometer must be accurate. The tension measurement must precede the dynamometry, as the pressure on the globe during the latter test, reduces the intra-ocular tension, a fact too well known to require further mention.

4. *Application of the dynamometer.* The observer should practice the procedure of holding the instrument horizontally, using the right hand for the left eye and the left hand for the right, and develop the ability to maintain the button always at the proper point of contact with the globe, which is just external to the insertion of the externus tendon, during the whole procedure by tactile sense alone without the necessity of looking at the instrument while the pressure is being applied. This is necessary because he must simultaneously observe the retinal arteries with his ophthalmoscope. He must particularly avoid allowing the tip of the gauge to ride back into the outer canthus behind the equator because pressure at that point will not give correct results.

5. *Ophthalmoscopy.* A direct image obtained with a self luminous ophthalmoscope is preferable; the May model is ideal for the purpose. The disc is located, clearly focused and an artery on the disc selected for intensive observation. It is essential that the artery observed be on the disc and not beyond it, where the vessel is covered with glial tissue and optic fibres. Should the artery be pulsating before any application of external pressure, the test for diastolic arterial pressure cannot be made because the intra-ocular pressure upon the artery is already greater than the pressure within the vessel.

6. *Combined ophthalmoscopy and dynamometry.* An artery on the disc being in clear view and the gauge properly in place, gradual regular pressure is exerted and very soon a pulse is seen in the artery. The first occasional beats are disregarded, the important thing is to determine the exact point where regular rhythmic pulsations commence. The observer then takes the reading on the dial where the indicator needle remains stationary, notes the findings, and rapidly resumes the combined pressure and observation until the pulsation is made to cease, when his second reading on the dial is noted. The determination of the exact point where the pulse is obliterated is more difficult than that of the establishment of the pulsation, but for-

tunately is of less importance in the present study. While no harmful results are reported, the originators of the system recommend that the maximum pressure never exceed 150 grams.

7. *Converting the gauge figures into terms of millimeters of Hg. on the chart.* This is done by following the curve of the tonometry figure to the point where it reaches the dynamometer figure and reading off the millimeters of Hg. at that level.

NORMAL RETINAL ARTERY PRESSURE

Having developed a certain facility in the combined use of the ophthalmoscope and the dynamometer we next proceeded to examine one hundred pairs of eyes, normal so far as ocular media and general blood pressure were concerned. These cases included individuals of both sexes, of varying ages from seven to fifty years, and all were done in the afternoon. We found the average diastolic pressure of the retinal artery to be 32 mm. Hg. and the average systolic pressure 70 mm. Hg. The lowest diastolic pressure in this series was 25, the highest systolic 95.

Where the difference in the two eyes was more than 10 grams with the dynamometer we knew we were in error and repeated the test. Magitot and Bailliart consider 30 to 35 mm. Hg. the normal diastolic and 70 to 80 mm. Hg. the normal systolic figures.

Some corroboration of Magitot's observation of the modification of the retinal arterial pressure in different states was found. It is less in children than in adults, less before than after meals, higher after physical exertion.

The retinal arterial pressure is conditioned by the general arterial pressure and normally depends directly and absolutely on the latter pressure and follows its variations.

A comparison of the diastolic retinal arterial pressure with the diastolic general arterial pressure discloses that a fairly constant ratio of 0.45:1 exists. For example, if the retinal pressure be 35 we divide 35 by 0.45 and obtain the figure 77 which will usually be found to be about the diastolic brachial pressure in the individual. Magitot goes so far as to state that, knowing the retinal he can determine mathematically the brachial pressure, and vice versa. Certainly our experiments, while not uniformly agreeing with this, do show a remarkable fixed relation between the two. In the comparison of the systolic retinal pressure with the systolic brachial pressure there is

wider variation but here too a definite relation seems to exist. Magitot uses the coefficient of 0.54:1 as the correct ratio.

We have not had enough experience to confirm his further statement that in high general arterial pressure the ratio for diastolic pressure is 50:1.

Proceeding now to the practical application of this test in cases of suspected or proved increased intracranial pressure, we made a series of experiments as to the possible disturbance of this normal ratio between the systolic retinal arterial pressure and the systolic brachial pressure. Table XI, representing ten consecutive clinical cases of cerebral neoplasm from the services of Dr. Charles A. Elsberg and of

TABLE XI

RISE IN RETINAL BLOOD PRESSURE IN TEN CASES OF CEREBRAL NEOPLASM

DIAGNOSIS	PAPIL- LEDEMA	DIASTOLIC RETINAL ARTERY TENSION	DIASTOLIC RETINAL ARTERY TENSION	DIASTOLIC BRACHIAL ARTERY TENSION	RATIO
1. Pre-operative brain tumor.....	3D	65	65	70	0.81:1
2. Pre-operative brain tumor.....	1D	65	65	78	0.83:1
3. Post-operative brain tumor.....	4D	50	50	90	0.55:1
4. Pre-operative brain tumor.....	2D	65	70	75	0.95:1
5. Pre-operative brain tumor.....	1D	80	80	85	0.94:1
6. Pre-operative brain tumor.....	2D	65	70	80	0.83:1
7. Pre-operative brain tumor.....	3D	60	65	98	0.63:1
8. Post-operative brain tumor.....		25	30	36	0.77:1
9. Post-operative brain tumor.....	4D	45	45	75	0.60:1
10. Pre-operative brain tumor.....	1D	60	60	98	0.61:1

Dr. Israel Strauss at the Mount Sinai Hospital, is illustrative of the rise in retinal blood pressure.

These ten cases represent but a small number of the total examined, but they suffice to bring out the change in ratio.

Magitot and Bailliart do not, in any of their reports attempt to specify the border line in the disturbance of the ratio between the retinal and the systemic pressure, beyond which one may state definitely that increased intracranial tension exists. In the cases they report, they content themselves with stating that an "inversion" of the normal ratio exists. It seems advisable to us from our experiments to attempt to specify such a border line, even though this be somewhat arbitrary and susceptible of modification after further

study in a larger group of cases. We would, therefore, from our experience to date, state that when the ratio of the diastolic retinal pressure to the diastolic brachial pressure is as 80 or more to 1 we may consider the intracranial pressure abnormally high.

On this basis we have found that the ratio was thus disturbed always when the patient presented other definite evidence of intracranial hypertension. We have seen it also without papilledema. An interesting observation is that in the early stages of papilledema, the ratio is higher than in the later stages. Another fact of significance is that the ratio often drops towards normal in the presence of a persistent or increasing papilledema, which bears out the common belief that the degree of papilledema is no criterion of the degree of increased intra-cranial and that normal intra-cranial pressure may be present with marked or increasing papilledema. This is especially true after craniotomy.

CONCLUSIONS

1. Routine examination of the retinal pulse by the method of Magitot and Bailliart, with due care, gives fairly constant normal figures. Whether these figures actually represent the exact diastolic and systolic blood pressure or not, they nevertheless are constant enough to be taken as a basis for comparison with the general blood pressure.

2. A normal ratio of 0.45 to 1 exists between the diastolic retinal arterial pressure and the diastolic brachial arterial pressure.

3. Where this ratio is raised to 80 to 1 or higher, there is increased intracranial pressure.

4. Routine use of this method with perfection of technique should give an added and perhaps even an independent proof of the existence of increased intracranial pressure.

DISCUSSION

The following questions submitted to Dr. Barnert before the Commission, together with the answers to them, are here reported verbatim.

DR. E. W. TAYLOR: Exactly where is the button of the instrument placed?

DR. BARNERT: The button of the instrument is placed directly in contact with the conjunctiva over the sclera, external to the limbus, not on the cornea. If placed on the cornea it would interfere with the observation of the fundus.

A simple method of seeing this pulse is to look at the fundus and make digital pressure through the upper lid. In any case there were some of the older observers who thought that they could determine roughly whether a patient had increased blood pressure by the time it took to establish the pulsation with the finger on the eye.

DR. AYER: I should like to ask if by any chance you have used this in connection with the oculocardiac reflex?

DR. BARNET: I have not. There are many angles to this subject. What I was interested in in particular was checking the figures of Magitot and Bailliart as to the change of this ratio in increased intracranial pressure.

DR. KENNEDY: It might be permitted under the new ruling for me to make a remark regarding an experience I had two and a half years ago. A patient was brought to me by two oculists who had told the individual that on the basis of readings by this method he had increased intracranial pressure and an occipital lobe tumor. The man certainly had no brain tumor. If he had an increased intracranial pressure it was not discoverable by neurological methods, and he has remained in good health since then.

I think it is wise to be careful about drawing large conclusions from single readings by instruments of precision. Do you not think so?

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CHAPTER XVIII

THE RELATION OF THE TENSION OF THE EYEBALL TO THE FIRST APPEARANCE OF PAPILLEDEMA

WALTER R. PARKER, M.D.

THE subject matter herewith presented, on the relation of the tension of the eyeball to the first appearance of papilledema, is based on the material used in three former publications, and also on the results observed in forty additional proved cases of brain tumor.

In the first paper, published in 1911,¹ six cases showing symptoms of intracranial tumor with choked disks were studied by comparing the amount of swelling in the nerve head with the tension of the eyeball. In two cases, the swelling was equal in the two eyes and the tension was the same in both eyes. In two, the disk was higher in the eye of lesser tension. In one, the swelling was higher in the eye of greater tension, but the process was older in the softer eye. One case showed a difference in tension of 5 mm. Hg. but there was no marked difference in the appearance of the nerve heads, each being swollen from 4 to 5 D.

Based on the clinical observations made on these six cases, the following suggestion was made:

If the tension of the two eyes is the same, the edema will appear at the same time in each eye, but if the tension of the two eyes be of a different amount, the edema will appear first, other things being equal, in the eye showing the lesser tension."

In the second paper, published in 1916,² the results of the experimental studies, conducted for the purpose of checking the suggestion originally made, were presented.

¹ Standish, M.: The mechanics of choked disk. *Ann. Ophth.*, 1911, xx, 711.

Parker, W. R.: The relation of choked disk to intra-ocular tension. *Ibid.*, 715.

² Parker, W. R.: The relation of choked disk to the tension of the eyeball. *J. Am. Med. Assn.*, 1916, lxxvii, 1053.

The experiments were conducted by diminishing the tension of one eye in dogs and monkeys and inducing increased intracranial pressure by artificial means. In each instance the pressure on the brain was made on the side opposite the eye with the lesser tension. The experiments went to a satisfactory conclusion in nine dogs and three monkeys. In every instance, except when a saline solution was used, the swelling appeared first in the eye of lesser tension. The results in one of the monkey experiments were so interesting that I shall report it in detail.

Monkey experiment 1. Small Brazilian monkey, estimated refraction emmetropic, tension each eye 18 mm. Trephine operation performed on right eye. Tension after operation 6 mm. Under ether anesthesia the skull was trephined over the left occipitoparietal region and a piece of sponge tent 8 by 7 by 3 mm. was introduced between the bone and the dura.

On the second day there was a marked edema of the right disk, the left remaining normal. On the sixth day the tension was 15 in the trephined eye and all evidence of edema had disappeared. On the seventh day the trephine operation was repeated on the right eye. On the fourteenth day a second piece of sponge tent 11 by 8 by 2 mm. was introduced in the region of the first operation. On the second day thereafter, the disk in the right eye was swollen 2 D., left, normal. On the fourth day the right disk was swollen 4 D., left normal. The papilledema in the right eye remained stationary at 4 to 5 D. for ten days, and then gradually receded until the fifth day it was 2 D. While the left eye showed slight edema there never was present a measurable swelling of the disk. At this time the tension was right eye 19, left eye 25. Twenty-seven days after the last implantation, the trephine operation was repeated. Tension lowered to 3 mm. Five days thereafter, without further implantation, the disk in the trephined eye again reached 4 D., while that of the left was at 0, where they still remain.

In figure 89 is shown the photomicrograph of the normal optic nerve in a dog. Figure 90 illustrates the papilledema produced in a dog by artificially increased intracranial pressure. Figure 91 illustrates the same in the monkey. Figure 92 is a photomicrograph of the optic nerve of a dog with a choked disk after intracranial injections of saline solution under pressure.

A saline solution under registered pressure was injected through the trephine opening after the dura and arachnoid had been divided. The tension in the left eye was made negative by a sclerocorneal trephining operation. At a pressure of 30 mm. of mercury, the right disk was swollen 2 D., the left 3 D. At 55 mm. pressure, each eye was swollen 6 D. At a pressure of 80 mm. an exophthalmos developed in the right eye, and, at the same time, a tremendous edema of the nerve and retina in the left eye, but no proptosis appeared. At a pressure of 110 mm.

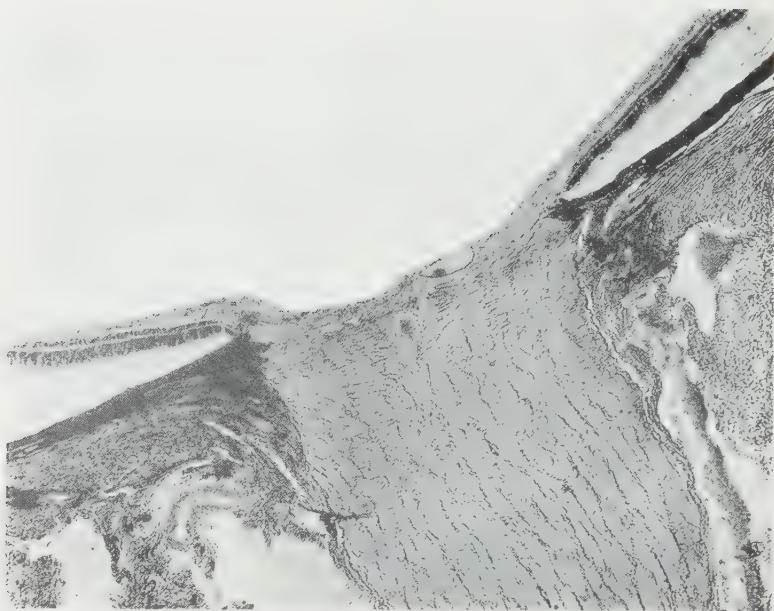


FIG. 89. Normal optic nerve in dog

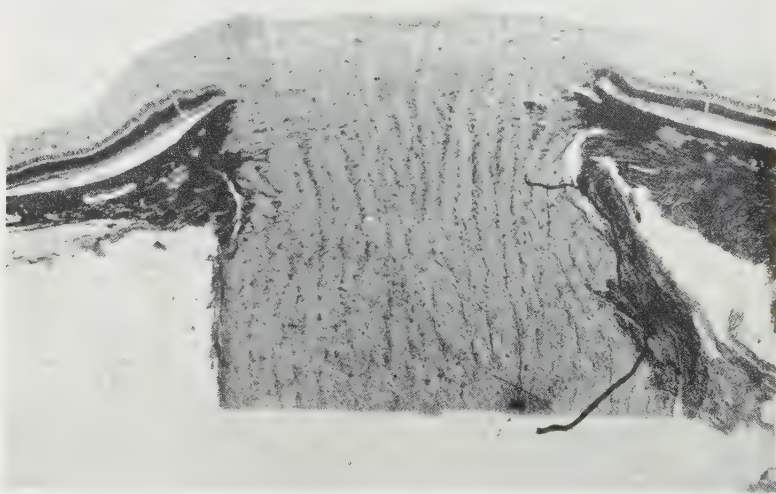


FIG. 90. Papilledema in dog produced by artificially increased intracranial pressure.

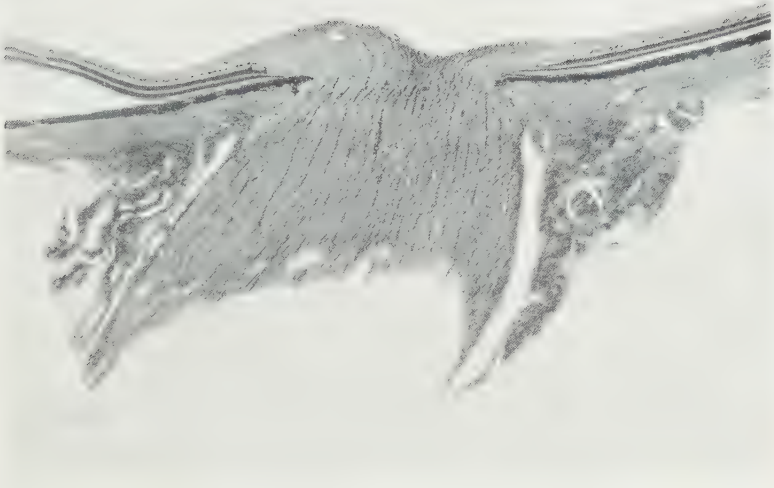


FIG. 91. Papilledema in monkey produced by artificially increased intracranial pressure.

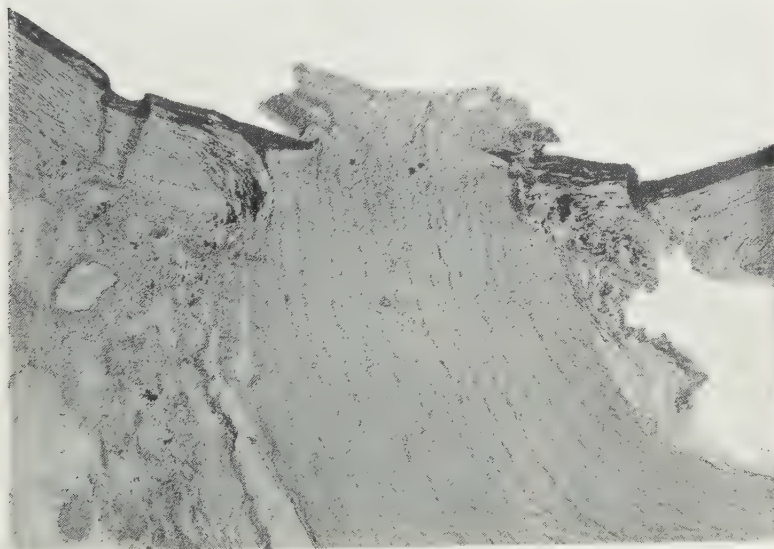


FIG. 92. Photomicrograph of choked disk produced by injections of saline solution through trephine opening in the skull.

the dog died. There was practically no difference in the amount of swelling in either eye at any stage of the experiment.

In the third paper, published in 1924, the experimental work was reviewed and a clinical study made of twenty-three proved cases of brain tumor. In this group of twenty-three cases, 78.2 per cent bore out the theory that choked disk in cases of intracranial pressure manifests itself first in the eye with the lesser tension, or, in cases in which the tension of the two eyes is the same, both disks become involved at the same time to an equal degree. To this list of 23 cases are now added 40 others, making a total of 63, all proved cases of brain tumor.

The cases may be classified in groups as follows:

<i>Group I.</i> Cases showing a greater degree of papilledema in the eye of lesser tension.....	20
<i>Group II.</i> Cases showing an equal amount of papilledema with the tension the same in the two eyes.....	18
<i>Group III.</i> Cases showing the greater amount of papilledema in the eye of higher tension, process older in softer eye.....	7
<i>Group IV.</i> Cases showing the same degree of papilledema with a different degree of tension in the two eyes.....	9
<i>Group V.</i> Cases showing a different degree of papilledema with the same tension in the two eyes.....	6
<i>Group VI.</i> Cases showing the greater degree of swelling in the eye of higher tension, process same in both eyes.....	3
Total.....	63

The number of cases that conform to the assumption that papilledema appears first in the eye of lesser tension or at the same time and to an equal degree in eyes of equal tension, is determined by adding together the number of cases in groups I, II, and III; total of 45 or 71.4 per cent.

The number of cases showing a difference in tension in the two eyes is determined by adding together the number of cases in groups I, III, V and VI. Total 36 or 57 per cent.

In table XII are given the clinical results obtained in the 63 cases, together with the revised results that would have been obtained if all the cases in which there was a difference of swelling of 1D. were classified as having the same amount of papilledema in the two eyes; and if all cases with a difference of tension of not more than 2 mm. of Hg. were recorded as equal in the two eyes.

While the results of the experiments are most convincing, confirmatory clinical evidence that the onset of choked disk is in the eye of lesser tension, is not always so satisfactory. The uncertainty of taking accurate readings of tension of the globe, the lack of opportunity for making an early observation in brain tumor cases, together with the great difficulty in differentiating the inflammatory from the edematous changes, and the early from the late changes in the nerve head, all contribute to the complication of the problem. Again, an eye that may show an initial lower tension, may later, in the presence of an edema of the nerve head, with hemorrhages, show a secondary glaucoma that will result in a reversal of the relative hardness of the

TABLE XII
CLINICAL RESULTS OBTAINED IN 63 CASES

	AS RECORDED	AS REVISED	TOTAL AS RECORDED	TOTAL AS REVISED	PER CENT AS RECORDED	PER CENT AS REVISED
Greater swelling softer eye.....	20	13				
Equal swelling equal tension.....	18	35	45	53	71	84
Process older softer eye.....	7	5				
Difference of swelling in the two nerve heads.....			36	22	57	34
Difference in tension in the two eyes.			39	25	61	39

eyes. It is needless to say the figures given are not absolute and many more observations must be made to establish the clinical facts.

The frequency of occurrence of a difference of tension in the two eyes in the normal individual is quite different according to published reports. Marx found in a study of eighty-three pairs of normal eyes, the tension different in 61.4 per cent.

Apparently, a difference in the tension of the two eyes is a determining influence in the onset of choked disk only in that it may indicate which eye will be first affected. The eye first affected need not necessarily be the one in which the disk shows the greater swelling at the time of observation. When both disks are affected, the one in the softer eye may show an older process with less degree of swelling than that seen in the nerve involved later.

The cases herein published are from the Neuro'logical Service in the University of Michigan and I am indebted to Dr. Peet for the privilege of reporting them. I wish also to express my appreciation of the services rendered by Dr. Eugene Vernou who assisted in the compilation of the case records.

DISCUSSION

The following questions submitted to Dr. Parker before the Commission together with the answers to them are here reported verbatim.

DR. TIMME: In these brain tumors that apparently produce swelling of the disks contrary to rule, was there any actual designation of the locality of the tumor? For instance, were any of those tumors, particularly in the prefrontal region of the side in which the swelling first appeared contrary to rule, of the type at one time described by Dr. Foster Kennedy, "Expanding tumors of the frontal lobe" producing swelling on the ipsilateral side before the other side became involved?

DR. PARKER: In my experimental work the artificial tumors were all extradural, and varied in position from before backward. In every instance they were introduced on the side opposite the trephined eye, and invariably the swelling of the nerve head appeared first in the softer eye.

In regard to the group of cases of "Expanding tumors of the frontal lobe" with resultant optic atrophy on the side of the tumors and choked disk on the other side, a possible explanation of the occurrence is, the location of the tumor is such that it exerts a pressure on the sheath of the optic nerve with a resultant descending atrophy. While the increased intra-ocular pressure produces a choked disk in the opposite side on which the sheath is patulous.

DR. KENNEDY: I take it, Dr. Parker, from your work that papilledema can occur more quickly in an eye with lowered tension. One could not draw final conclusions, however, from the tone of an eyeball without regard also to the refractive condition. A papilledema will occur more quickly in an hypermetropic eye than in a myopic eye, so other factors than simple tension determine the earlier or later incidence of papilledema—I mean other factors in the eye itself, apart from the pressure within the skull. Is that an uninformed remark from an ophthalmologist's point of view?

DR. PARKER: No comparative study of the effect of the refractive error on the incidence of papilledema was made in our experimental work as all the animals either had normal eyes or were hyperopic.

In regard to the infrequency of papilledema in myopia there is still some difference of opinion. The generally accepted view is that patients with high myopia rarely have choked disk. Mr. Leslie Paton holds that this is not true. I have felt that it did occur less frequently, but I have no definite statistics to substantiate this view. If papilledema does occur less frequently in cases of high myopia, a possible explanation might be that the tissue in the lamina cribrosa is put on the stretch, and would, therefore, offer more resistance. Also in myopia these may be an atrophy of the tissues over the nerve head.

CHAPTER XIX

THE FUNDUS CHANGES AND THE BLOOD PRESSURE IN THE RETINAL ARTERIES IN INCREASED INTRACRANIAL PRESSURE¹

PAPILLEDEMA AND OPTIC ATROPHY

CONRAD BERENS, M.D.

IN THE study of general diseases and particularly diseases of the nervous system, the ophthalmoscope is becoming increasingly important. As all the tissues ordinarily seen with the ophthalmoscope are direct extensions of brain tissue, or are derived from the cranial cavity, we may speak of ophthalmoscopy in a sense as cerebroscopy, a term introduced by Eugene Bouchut in 1893.

The great value of the ophthalmoscope in the study of diseases of the nervous system was first appreciated in 1859 by von Graefe, and at practically the same time by Businelli of Rome. These observers noted papilledema in relation to brain tumor, a physical sign which is now recognized as of great importance. That this sign is usually seen late rather than early in the course of cerebral tumors has been stated by Elsberg (1) and recently reemphasied by me (2). Thanks to the invention of the ophthalmodynamometer by Bailliar (3) and to his keen observation we now have an additional diagnostic refinement by which it may be possible to detect increase of intracranial pressure before choked disc is noted, or before other definite signs of increased pressure can be determined with the ophthalmoscope.

ONSET AND DEVELOPMENT OF OPHTHALMOSCOPIC SIGNS OF INCREASED CEREBROSPINAL FLUID PRESSURE

Symptoms of increased intracranial pressure are slight in many cases and the swelling of the disc may even precede headache, so that the earliest fundus changes, namely, hyperemia and edema (Knapp) or congestion with edema (Gowers), may not be seen. In the first

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stage, according to de Schweinitz and Gunn, the upper or lower margins of the disc are usually the first to be blurred and this change then extends to the nasal side. Even if this stage is noted there are so many physiologic variations in the size of the blood vessels, the color of the nerve head and the appearance of the nerve margins that one should hesitate to diagnose increased intracranial pressure from the ophthalmoscopic examination alone, unless the fundi have been examined periodically. It is important to realize that greatly increased intracranial pressure is frequently unassociated with ophthalmoscopic signs other than those determined by the use of the ophthalmodynamometer and the study of the diastolic pressure in the retinal arteries, as compared with the brachial diastolic pressure.

Following the earliest changes of congestion and edema the disc assumes the appearance of an ordinary beginning neuritis. If there is a physiologic excavation, usually grayish white in color, it assumes a pink hue which deepens to red as the swelling tends to obliterate the depression, and the altered color makes the area of the physiologic cup indistinguishable from the rest of the nerve head. The nerve margins become blurred and, at times, there seems to be a delicate veil which masks the finer details.

The first change usually discovered in the blood vessels is slight fullness of the veins, suggesting interference with the return circulation. A keen observer may then note increased tortuosity. If venous pulsation has not been present, this may become evident, but ordinarily no change can be detected in the arteries. The circumpapillary area of the retina may be slightly cloudy, but at this stage there is generally no appreciable swelling of the disc. However, in certain cases the disc becomes edematous before hyperemia is noted. In some instances the swelling of the disc occurs rapidly and progresses to the maximum in a few days. In other cases, a swelling of $\frac{1}{2}$ to 2 diopters may persist for weeks or even months without producing permanent visual disturbance.

A striking example of this was seen in a woman (case 1, G. C. D.), 51 years of age. This patient, who was seen by Doctor Cushing in consultation, had unilateral papilledema, which persisted for two years with no loss of vision, chronic interstitial nephritis, apical dental infections, possible sinus infection, probable pituitary tumor (as shown, by two roentgenograms) and signs of brain tumor or arachnoiditis. The papilledema was apparently unimproved by the extraction of the infected teeth or by nasal treatment, spinal puncture or drugs. Mixed

catarrhal vaccines seemed to be beneficial, perhaps by a nonspecific protein effect or by a specific action on bacteria in the nasal sinuses or in some undiscovered focus of infection. Possibly the injections of vaccine have had nothing to do with the improvement, and the patient may have a brain tumor which will cause trouble later.

This case points to the difficulty of diagnosis even in unilateral papilledema. It emphasizes the possibility that operations might

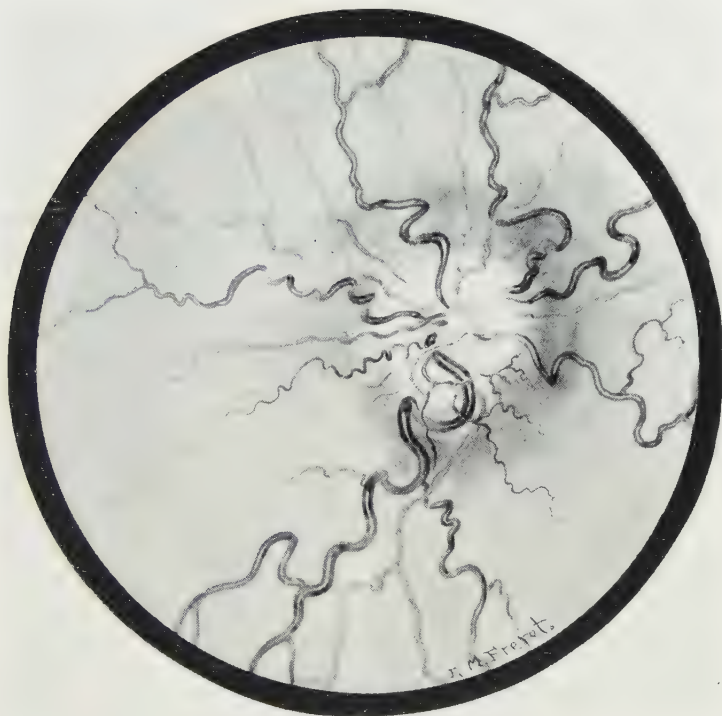


FIG. 93. Papilledema of 3 diopters in a patient with increased pressure of the cerebrospinal fluid, 480 mm. of water at the time the drawing was made.

sometimes be done too early, and teaches us that with patience and careful observation an operation may eventually prove unnecessary, for after two years this patient has 20/15 vision in each eye, and normal visual fields. However, the ophthalmologist must sometimes suggest decompressive measures in the absence of localizing signs and

he should base his decision on close observation of the vision, fundi, retinal blood pressure and quantitative visual field studies.

Another patient (case 2, Miss E. T.), 36 years of age, had bilateral papilledema of 3 to $3\frac{1}{2}$ diopters which persisted for nine months. The visual acuity never decreased below 20/30 in either eye. This case was also complicated by chronic ethmoiditis and apical dental infections. The hemorrhages and exudates made two consulting ophthalmologists believe that the condition was due to some toxic factor rather than a brain tumor, but elimination of foci of infection had no effect on the papilledema, although the hemorrhages became less numerous and finally disappeared. The retinal diastolic pressure was at first high, 60 mm. Hg nearly equaling the brachial diastolic pressure of 70, but finally fell to 35 mm. Hg, although the spinal fluid pressure was 480 mm. of water.

The fall of the retinal pressure when papilledema is established with increased intracranial pressure has also been noted by Magitot (4) and Kalt (5). Some authors, notably Uhtoff, regard a swelling under 2 diopters in height as more likely to be due to neuritis than to mechanical edema, but I agree with von Hippel that this hypothesis is open to criticism. I believe that in all cases of papilledema there must be an early stage in which the swelling is under 2 diopters, and naturally at this time it is most important to make an accurate differentiation.

Elsberg's (1) figures in regard to the presence and degree of papilledema at the time of the first examination in cases where brain tumor was found at operation or at autopsy are of interest in this discussion. The fundus was normal in 24 cases. There was papilledema of 1 diopter in 6; 1 to 2 diopters in 11; 3 to 4 diopters in 13, and 5 to 6 diopters in 9.

In spite of the apparent simplicity of the matter, as outlined in text-book descriptions and in the statements of some authors, I find differential diagnoses extremely difficult to make, even by every available diagnostic method. This applies not alone to swelling of the disc below 3 diopters, but also to 7 or 8 diopters of swelling.

Conceding the validity of Cushing's (6) statement that over 4 diopters of elevation must be caused by mechanical pressure, it does not necessarily mean that the pressure of the cerebrospinal fluid must be lowered by direct means. Sluder has apparently cured a case of papilledema of over 5 diopters by operation on the sphenoid sinuses. Bell (7) reported a case of bilateral papilledema of 8 diopters which was probably due to empyema of the sphenoid and ethmoid sinuses,

as it was evidently cured by opening the ethmoids and sphenoids, and in a personal communication he stated that "there has been no recurrence of the edema for nine years."

It is evident that the onset of the swelling of the disc may occur in various ways. Schieck believes the earliest phenomenon in papilledema is blurring of the center of the papilla, where the large vessels emerge. Horsley, on the other hand, maintains that the swelling always begins in the upper nasal quadrant. Von Hippel agrees with neither of the authorities, but states that the papilla has a definite mushroom-head appearance, with raised edge and deep central cup, in the earlier stage.

It is not definitely known why the papilledema is usually limited to 7 or 8 diopters of elevation as compared with the normal fundus level, but it may be due to the inability of the fibers of the disc to stretch further. It is well known that each diopter of swelling corresponds approximately to one-third millimeter of actual elevation of the disc, as determined by the direct method, and also that the actual swelling seldom exceeds 3 mm. With the indirect method and inverted image the swollen disc exhibits parallax displacement if a slight to-and-fro movement is made with the condensing lens, that is, the most elevated areas are displaced more rapidly than the others.

At the same time that papilledema appears, the disc loses its physiologic aspect, its diameter may double and its margins cover the neighboring retina and choroid. The disc frequently takes on a yellowish tint, losing some of its red, congested appearance. It seems as though there were red and yellowish rays extending from the center of the papilla. This appearance is probably produced by edematous enlargement of the nerve fibers and by dilatation of the capillaries, both arterial and venous.

With red-free light, particularly when the large Gullstrand ophthalmoscope is used, the nerve fibers may be seen to be widely separated about the disc; some of the rays are larger and redder than the others. These are usually the veins, as the arteries on the disc are small and difficult to see, so that it is almost impossible to determine their point of origin. Around the disc, the vessels are obscured by a gray edematous veil. Outside of this edematous area the vessels can be clearly seen, are usually dilated, dark red in color and frequently tortuous. The veins may even seem more numerous than normal, usually owing to engorgement of the smaller vessels that are not ordinarily visible.

It has been stated that in the earlier stages, the arteries are normal, but in the later stages, they are small, depressed below the surface of the surrounding tissues, and frequently have a gray contour which gives the appearance of periarthritis. In attempts to determine the pressure in the arteries at this stage of the process, it is frequently difficult to note their pulsation.

There may be considerable variations from the foregoing description, often the appearance of radiating striae is lacking, the disc being uniformly red, although its color may vary from dirty gray to orange-yellow or deep red. As hemorrhages and exudates may completely change the picture, depending upon their position and number, we speak of them last. Although the retina frequently remains normal, this is particularly true in the early stages; if careful study is made, especially with red-free light, hemorrhages are often observable.

Hemorrhages are usually superficial—being frequently located in the nerve fiber layers, where they naturally assume a flame shaped appearance. As their long diameter is in the same axis as the blood vessels, and they often occur in contact with the blood vessels, they may be difficult to find. In some cases, instead of being in association with the blood vessels, particularly with the veins, they may completely surround the disc, or may be on the disc.

Small exudates are also frequently seen, as light gray, irregular veils covering the retina or disc; if they are large and dense, they appear white and hide the underlying blood vessels. Although the hemorrhages and exudates are usually localized in the region of the disc, they may be scattered throughout the fundi, as in the so-called "retinitis of diabetes" and "retinitis of nephritis" but rarely occupy the region of the macula. Some authors have attempted to attribute great importance to the hemorrhages and exudates in the diagnosis and prognosis of brain tumors, but my experience has not shown that the prognosis is more grave if the hemorrhages are large and numerous, or better if they are absent.

OCULAR SYMPTOMS OF INCREASED INTRACRANIAL PRESSURE

A very important point to remember in diagnosis is the fact that visual acuity may be unaffected in papilledema even of long standing, and that there may be no symptoms or signs of papilledema which can be discovered without the use of the ophthalmoscope.

One patient (case 2) who had bilateral papilledema of 3 diopters

for nine months maintained vision of 20/20 in the right eye and 20/30 in the left. When visual acuity is affected, the onset is usually gradual, and attacks of slight blurring of vision are complained of at first. These may occur at intervals of one to several days, and in this case, there were 7 to 15 attacks a day for several months. Later the blurring of vision may become more severe and last for one to fifteen or twenty minutes or longer. During the attacks the vision may fail almost completely, but usually it returns rapidly. The period of these attacks is called the "phase of obnubilation" by Dupuy-Dutemps (8), who believes it is a characteristic symptom of brain tumor.

COURSE OF PAPILLEDEMA AND SECONDARY OPTIC NERVE AND FUNDUS CHANGES, INCLUDING SECONDARY ATROPHY

Sometimes papilledema persists for months or years, but frequently the swelling begins to subside in a few weeks. Improvement is not always progressive, as exacerbations of the symptoms of increased cerebrospinal fluid pressure, including papilledema, may recur at intervals. As the swelling subsides the color of the disc generally changes to a more grayish hue and its outlines become more pronounced. If the radially arranged striae have been prominent they disappear as the congestion of the veins decreases and the arteries are more visible. Even when the acute process has abated there may be slight elevation of the disc, frequently $\frac{1}{2}$ diopter, and its margins are usually indistinct. There is usually a characteristic gray pallor of the disc, although the veins may still be somewhat engorged and tortuous. Atrophy of the nerve commonly results, due to compression of the nerve fibres, but vision is seldom completely lost. In some cases, as in one reported by Jackson (9), the edema subsides without affecting visual acuity. In other cases edema may recur as the result of the same or another lesion; recurrence of papilledema of 5 diopters has been seen by de Schweinitz and Thomson (10) thirteen months after palliative decompression, where postneuritic atrophy was present. I have seen one patient in whom 3 diopters of swelling of the nerve subsided without leaving demonstrable ophthalmoscopic evidence of its previous existence. The cause of papilledema was never definitely determined.

If the pressure of the cerebrospinal fluid is lowered by operative measures, the edema may subside rapidly; even though cure of the

underlying disease is not affected. Vision may be conserved if it has not been seriously disturbed and if further compression of the nerve can be avoided. Even if vision has been seriously affected, operation may sometimes restore useful vision. I have seen one patient who had light perception only, read large print two days after operation, the edema of the nerve having subsided markedly on the day of the operation. Rapid subsidence of the edema has been noted experimentally by Cushing and Bordley (11).

Apparently the first observation in regard to the subsidence of papilledema following trephining was made by Sir Victor Horsley (12) in 1890. Röhmer and Dupont noted cure of papilledema after

TABLE XIII
OPTIC NEURITIS AT VARIOUS AGES IN CEREBRAL AND CEREBELLAR TUMOR
(SINGER (13))

AGE IN YEARS	NUMBER OF CASES	OPTIC NEURITIS (PERCENTAGES)				
		Well marked	Late or slight	Chronic	Doubtful	Absent
Under 30	35	97.1	2.9			
30 to 40	18	76.6	2.2	1.1		1.1
40 to 50	21	61.9	4.3	4.8		19.0
50 to 60	7	28.5	57.1			14.3
Over 60	7		14.3		28.5	57.1

trephining for decompression in 28.56 per cent, improvement in 42.75 per cent and no improvement in the remaining cases. One might be inclined to think that papilledema would be caused by increased intracranial pressure, as frequently in patients of advanced age as in the young, but in patients with brain tumor, Singer (13) has apparently shown that this is not the rule (see table XIII).

Several authors have attempted to divide the changes seen in papilledema into stages, and the arrangement made by Gunn (14), modified by de Schweinitz and Holloway (15) to which minor changes have been made, summarizes the description which has been given:

First Stage

Hyperemia of the disc, blurring of its upper and lower margins and gradual progression of the blurring to the nasal edges while the temporal margin is still visible. Diastolic blood pressure in the central

artery of the retina usually disproportionately increased over brachial diastolic pressure.

Second Stage

Increased edema of the nerve head, incipient filling in of the physiological pit, involvement of the temporal margin of the disc, with a tendency of the edema to spread into the surrounding retinal area, and uneven distention and darkening of the retinal veins.

Third Stage

Decided increase of edema, elevation and size of the nerve head. Vascular striation of the swollen tissue and striae of edema in the form of lines in the swollen retina between the disc and macula. Marked distention of the retinal veins and retinal hemorrhages. Retinal diastolic arterial blood pressure may or may not be abnormally high in comparison with brachial diastolic blood pressure.

Fourth Stage

Increase in the prominence of the disc, which assumes a mound shape and begins to lose its congested appearance becoming opaque. Exudation in and on the swollen disc and surrounding retina with elaboration of the retinal hemorrhages in size and number.

Fifth Stage

Decided subsidence of the vascularity of the papilledema and increasing pallor of the nerve with or without sinking of its prominence. Apparent contraction of the retinal arteries and thickening of their perivascular lymph-sheaths, making it difficult or impossible to determine retinal blood pressure accurately. Spots of degeneration of the retina, especially in the macula, represent the fifth stage, which passes into the final or sixth stage of so-called "papillitic atrophy."

For making the examinations it is important to have an ophthalmoscope which gives even illumination of the fundus for general study, concentrated light on the disc in determining retinal blood pressure, red-free light with sufficient illumination to observe details, and some means of accurately measuring the size of vessels. Paton (16) has stressed the importance of operation as soon as the size of the arteries begins to diminish. These features may be found in the combination of the Morgan (17) graticule with the Keeler ophthalmoscope. In

measuring the degree of edema it is first necessary to know the normal fundus level and to determine this it is well to focus on one of the small vessels temporal to the macula, one in the macular region, and then one on the most prominent part of the swollen disc. As the edema may involve the macula it is necessary to make three readings if mistakes are to be avoided.

HISTOPATHOLOGIC CHANGES WHICH PRODUCE THE OPHTHALMOSCOPIC SIGNS OF INCREASED INTRACRANIAL PRESSURE

We are indebted to Parsons (18) and to Paton and Gordon Holmes (19) for the most comprehensive and thorough study of the pathologic changes in the optic nerve in papilledema. From the pathological standpoint simple edema seems to be the most important factor, as the fluid in the tissues produces the swelling of the disc which obliterates the physiologic cup, separates the nerve fibers which possibly accentuate the striation, makes folds which appear as fine striations concentric with the disc margins, produces blurring of the disc and surrounding retina due to dispersion of light, and finally narrows the lumen of the arteries of the disc by direct compression thus adding to the engorgement and tortuosity of the veins by retarding return circulation. The venous stasis may be a factor in the production of hemorrhages which are flame shaped in the nerve fiber layer and tend to be more circumscribed, the more deeply they are placed in the retina. Signs of inflammation of the intraocular portion of the optic nerve are surprisingly few or entirely absent even in septic meningitis, but in some cases and when the condition has persisted for a long time, round cell infiltration may be noted in the walls of the blood vessels. This infiltration may account for the gray streaks along the vessel walls on the disc although they are probably due partly to thickening of the walls. The nerve fibers may also undergo degeneration; they first become swollen and this accounts in part for the striation around the disc. Then the nerve fibers break up into degenerative masses, the so-called "cytoid bodies" which according to Parsons undergo lipoid degeneration and ultimate absorption. These products of nerve fiber degeneration are supposed by some authors to be the sole cause of the white areas observed around the disc, but I have seen them appear early when the hemorrhages were first noted, disappearing as the hemorrhages were absorbed, and I believe that some at least are due to exudates. In some cases when the pressure decreases before



FIG. 94. Optic nerve showing edema in a case of metastatic sarcoma of the brain.



FIG. 95. Optic nerve in so-called "retinitis of nephritis." The edema and hemorrhages in the nerve head are clearly visible and the distention of the dural sheath of the optic nerve and the absence of inflammatory signs may be noted.

atrophy ensues, there may be little histologic change. If atrophy develops, the pallor is accounted for histologically by increase in the neuroglia and perivascular tissue, atrophy of the larger vessels, obliteration of the capillaries and diminution in size and possibly in number of the nerve fibers.



FIG. 96. Optic nerve showing edema of nerve in patient with brain abscess and meningitis. Edema, but no inflammatory changes in the intraocular division of the nerve although there is inflammation of the leptomeninges.

Through the courtesy of Dr. Wm. V. Cone of the Presbyterian Hospital, histologic examinations have been made of the optic nerves in a case of uncomplicated brain tumor, in one of so-called "retinitis of nephritis" and in a case of a temporal lobe abscess complicated by

streptococcic meningitis. The intraocular division of the optic nerves shows papilledema clinically and microscopically. In each case the area immediately overlying the optic nerve entrance showed the same type of swelling of tissues without inflammatory signs. The arteries of the retina and chorioid had undergone advanced angiosclerotic changes in the case of renal retinitis, and there were hemorrhages and exudates in the retina, and hemorrhages in the intraocular division of the optic nerve. The retina of the patient with meningitis was normal, but there were marked signs of perineuritis with lymphocytic infiltration of the leptomeninges. In these three cases the picture in the intraocular division of the nerve was that of infiltration of tissues with non-inflammatory fluid, and one would suppose the cause to be the same in each (figs. 94, 95 and 96).

PATHOGENESIS OF PAPILLEDEMA

The picture presented by these nerves, the rapid development and subsidence of papilledema clinically and experimentally, and the fact shown by Parker (20, 21) that the edema of the nerve head is usually greater in the eye with the lower tension, makes me believe that the mechanical increase in pressure of the cerebrospinal fluid is the most important single factor in the production of papilledema. Injection experiments (fig. 97) in animals conducted under the direction of Dr. J. E. Sweet, Department of Surgical Research, Cornell University, and the experiments of Gifford (22) and Wegefarth (23) have convinced me that there is lymphatic drainage from the eyeball along the central vessels, and it is my belief that blocking of this drainage is an important factor in the production of the edema. In some cases toxic products may be formed which tend to close these lymph channels, producing edema of the optic nerve, but final blocking of the lymphatics by atrophy from pressure may account for the late appearance of papilledema in some cases of brain tumor. There may be, and usually is, no increase in the intraocular pressure, as this is regulated by the chorioidal circulation through the vortex veins and by the escape of aqueous through the canal of Schlemm. We should attempt to account for the absence of papilledema in some cases where cerebrospinal fluid pressure is known to be high, as in hydrocephalus in children; and may not the blocking or freedom from blocking of the lymphatic drainage from the eyeball explain some of these cases?



FIG. 97. Section of optic nerve of cat. Eye enucleated three days after injection of 5 minims of trypan blue into vitreous chamber. Note staining of lymphatics around the central vessels and absence of stain in surrounding nerve fibers.

Liebrecht (24) was probably the first to suggest blocking of lymphatic drainage as the cause of papilledema, but Schieck (25) and Behr (26) also consider this an important factor. Paton and Holmes (19), although they believe it is a factor, consider it secondary to increased sheath pressure, and that venous engorgement is more important.

In my opinion, increased pressure in the sheath, if it is a sufficiently acute rise, may block lymphatic drainage from the vitreous, retina and intraocular division of the optic nerve and result in papilledema. If the increase in pressure is slow or of a chronic nature, readjustment of the circulation is made and papilledema may not result. Later, in chronically increased intracranial pressure from tumors of the brain and other causes, pressure atrophy may close the lymphatics, or toxic products of cell destruction may possibly produce sufficient inflammation to block the lymphatic drainage more completely. This hypothesis is strengthened by Wegefath's (23) experiments showing that lowering intracranial pressure, after intraocular injections, increases the depth to which the optic nerve and perivascular lymphatics are stained and that lowering intraocular pressure in one eye, before intracranial injections, facilitates the staining of the intraocular tissues.

Venous stasis in the branches of the central veins of the retina undoubtedly exists even though there is free anastomosis of the central vein with the orbital veins which do not empty into the cavernous sinus. Even though the pressure in the central vein is not apparently greatly raised in papilledema, as studied by the Bailliant method, the slight obstruction to circulation in the absence of increased intraocular pressure may be sufficient to account for hemorrhages and exudates. I believe the venous engorgement is not as important in producing the edema as the blocking of lymphatic drainage.

THE DIFFERENTIAL DIAGNOSIS BETWEEN THE OPHTHALMOSCOPIC
PICTURE PRODUCED BY INCREASED INTRACRANIAL PRESSURE
WITHOUT INFLAMMATION AND THAT OF PAPILLITIS AND
PSEUDOPAPILLITIS

In the early stages of swelling it is important to differentiate between papilledema, papillitis and pseudopapillitis—a differential diagnosis which will usually tax all the resources of the ophthalmologist, and neurologist. We are familiar with the facts that in the eye

with papillitis, the vision is apt to be diminished early out of all proportion to the degree of swelling (which rarely exceeds 1 mm. or 3 diopters, particularly if the papillomacular bundle is affected) and that in a patient with papilledema the vision may be very little affected for months and even years. The blood vessels in papilledema frequently show marked disturbance, the veins appear tortuous and the arteries are usually narrow; on the other hand in papillitis the arteries may be normal in size and show early signs of perivasculitis, whereas the veins are only slightly disturbed.

There are two other points that may be worthy of consideration. The first is the enlargement of the blind spot. In papilledema, this is usually not as great as in papillitis or proportionate to the degree of swelling of the nerve. The difference may be easily understood when we consider that in the first instance the enlargement is frequently only a mechanical condition due to the spreading aside of the rods and cones at the entrance of the optic nerve into the eyeball, while in papillitis the enlargement is due to the depressed function of the nerves themselves as the result of the action of some poison.

Study of the blind spot is extremely important in differentiating pseudopapillitis from papillitis and papilledema; in pseudoneuritis the blind spot is extremely small.

The early and differential diagnosis of papillitis and papilledema with the Gullstrand slit-lamp has been thoroughly studied by Koeppe (27, 28) and others. From their earlier work, this method would apparently have solved the problem of the differential diagnosis, but later studies have not entirely confirmed the original conclusions.

The second point is the disproportionate increase of the retinal diastolic blood pressure over the brachial diastolic pressure. This is more important in the early differential diagnosis for, as previously stated, when the edema is fully developed the retinal pressure frequently falls.

Even in unilateral swelling of the discs the differential diagnosis may be difficult, for we now know from the work of Kennedy (29) that subfrontal lobe tumors may sometimes cause unilateral choked disc, associated with the formation of a central scotoma and primary optic atrophy on the side of the lesion. Although unilateral choked disc is usually seen in diseases of the accessory sinuses, particularly the posterior ethmoids and sphenoids, and in diseases of the orbit such as abscesses and tumors, it should be remembered that tumors

and infections may extend into the orbit from the middle cranial fossa. I have seen one patient with unilateral papillitis apparently due to periapical dental infection and Langdon (30) a similar case due to infection in the tonsils.

In the differential etiological diagnosis, from the eye symptoms and signs of increased intracranial pressure, the following are a few of the conditions producing papilledema and fundus changes which should be considered:

1. Brain tumors

Pituitary disorders. Simple atrophy is most commonly encountered in pituitary disorders, but atrophy with what Benedict (31) describes as a "peculiar waxy pallor without shrinkage" is not infrequently seen. The waxy appearance of "pituitary atrophy" without shrinkage is attributed by de Schweinitz (32) to pressure without true atrophy. It should suggest the probability of fair visual prognosis, for de Schweinitz reports normal vision in both eyes in one of his (33) cases treated with thyroid extract. This patient had no light perception for twelve days in the right eye and for six weeks in the left eye, before the treatment with thyroid extract was begun. Lillie (34) believes that improvement in vision, following surgical intervention, is greatest in patients in whom the optic discs were normal in appearance, or in patients who had pallor of the disc without loss of substance.

Papilledema has been seen by Uhthoff (35) in 9 per cent of his collected cases. He finds papillitis or papilledema in 24 per cent of cases without acromegaly or trophic disturbances, and in 11 per cent of cases with such disturbances.

Papilledema was encountered in only three cases by de Schweinitz (36) in his series of 85 examinations which indicated only an intrasellar growth.

Cerebellar tumors. Papilledema is an early sign in tumors of the cerebellum and base. In 72 patients with papilledema as the result of brain tumor Kampherstein (37) found 32 per cent affecting the cerebellum. Edmunds and Lawford (38) found papilledema in 20 of 23 cases of cerebellar tumor.

Temporal lobe tumors. Bilateral papilledema is an early sign in tumors of the temporal lobes. Lillie (39) noted it in 43 of 60 verified lesions and found $\frac{1}{2}$ to 7 D. choking of the discs, as great on the con-

tralateral as on the homolateral side. He noted bilateral secondary optic atrophy in one case. The fundi were normal in 13 cases. He adds homonymous quadrant defects, either for colors or form, to the syndrome of Kennedy (40), which includes normal visual acuity and bilateral choked discs in early temporal lobe tumors.

Although, if present, papilledema is a valuable sign of brain tumor, its absence does not exclude tumor and it frequently occurs so late that valuable time may be lost if the surgeon waits for its appearance. A man was seen by Jackson (9) who had symptoms of brain tumor for nine years although papilledema occurred only one month before death. The autopsy confirmed the diagnosis of tumor. Cushing originally pointed out the danger of spinal puncture in the presence of a brain tumor and, Ayer (41) says, "It is questionable whether lumbar puncture should be performed where the presence of a tumor is highly probable." In the absence of papilledema then, unless retinal blood pressure is studied or the comparatively safe procedure of combined lumbar and ventricular puncture is performed, increased intracranial pressure may pass undetected. The finding of increased retinal blood pressure by Coppez (42) in the absence of papilledema, led to the early diagnosis and operative treatment of a patient with brain tumor.

2. *Brain abscess*

Papilledema is frequently seen in brain abscess. Gowers noted it in 75 per cent of cases where the abscess had been present for a month or longer, Kampherstein (37) collected 155 cases of brain abscess, and found optic neuritis in 37, hyperemia in 4, atrophy in 1, retinal hemorrhage in 2 and papilledema in 42. The location of the abscess seems to affect the incidence of papilledema, as White (43) found papilledema in 38 per cent of cerebellar abscesses and 60 per cent of temporo-sphenoidal abscesses of otitic origin.

In my experience, papilledema, unilateral or greater in one disc, if seen early in the disease, suggests the possible localization of the abscess on that side. However my findings have not been made in the light of Parker's (20, 21) work on the influence of the intraocular pressure on the degree of edema. The presence of unilateral papilledema should not be considered of great diagnostic value unless the tension of the eyes is equal or greater on the side of the more pronounced edema. The edema was unilateral in 13 per cent and was

on the side of the lesion in four-fifths of Uthoff's cases. When the edema was bilateral, it was greater *on the side of the lesion in four-fifths of the cases.* Penfield noted that the hemisphere of the brain affected by an abscess, even a small one, is greatly enlarged, a condition which is also observed in rapidly growing tumors. Possibly this fact might account for the early more pronounced edema on the side of the lesion, or if toxins are liberated they may first affect the nerve which is nearer the abscess.

3. Tumor equivalents

According to Horrax (44) this term should be applied to conditions simulating brain tumor, for which an intracranial operation is indicated just as positively as for tumor. These include:

a. Subacute or chronic cisternal arachnoiditis. (Serous or cystic meningitis). The etiology is unknown, but possibly the cause is a cerebral infection allied to poliomyelitis. It can be differentiated from tumor only by an exploratory operation or by encephalography.

b. Oxycephaly was the cause of papilledema in 2.2 per cent of Uthoff's series.

c. Pachymeningitis hemorrhagica interna.

4. Sinusitis

Seventy-five patients with sinus disease and optic nerve involvement were studied by White (45). Three showed papilledema of low degree, 2 to 3 diopters, and he suggests the term "optic neuritis with edema" to designate these swellings, reserving "papilledema" for describing edema of the disc caused by increased intracranial pressure.

Sluder speaks of 6 to 8 diopters of swelling in a patient with bilateral sphenoiditis. Bell (7) has seen a patient with bilateral ethmoiditis and sphenoiditis who had papilledema of 8 diopters in one eye and 9 diopters in the other with a few hemorrhages. In this case, normal vision with no recurrence of headache or edema for nine years followed bilateral opening of the sphenoid and ethmoid sinuses which contained pus.

Papilledema is not characteristic of optic nerve involvement due to sinus disease, but the differential diagnosis may be difficult. The nerves are most frequently involved in our experience in posterior ethmoiditis and sphenoiditis. Van der Hoeve and de Klein noted optic nerve involvement in 54 out of 59 patients. I have seen only

two patients in whom the enlargement of the blind spots, was apparently caused by infection in other sinuses. One patient had frontal sinusitis and another inflammation of the antrum, and there was pus under pressure in both instances.

Excluding diseases easily diagnosed ophthalmoscopically, for example, myopia, medullated nerve fibers and papilledema, the commonest cause of enlargement of the blind spots in our experience has been infection in the posterior ethmoid and sphenoid sinuses. We must not forget that glaucoma without characteristic cupping of the optic nerve can simulate sinusitis with involvement of the optic nerves, for six of the symptoms may be similar, namely, enlargement of the blind spots, paracentral and central scotomata, sluggish reaction of the irides with dilated pupils, blurred distant vision, and failure of accommodation. Quantitative perimetry and tonometry give us valuable differential diagnostic points.

5. *Arteriosclerosis*

Arteriosclerotic neuroretinitis may simulate closely renal retinitis, and in some cases sufficient edema of the optic nerve is present to make one suspect increased intracranial pressure. The marked sclerosis of the retinal vessels usually points to the correct diagnosis, although arteriosclerosis has been present in the eyes of all the patients suffering from renal retinitis that have been examined microscopically by me. Naturally the presence of arteriosclerosis does not exclude an intracranial lesion and increased intracranial pressure. Moore (46) re-examined the eyes of 52 patients who had retinal arteriosclerosis; after seven years 23 per cent had suffered from a gross vascular cerebral lesion as the result of which 17 had died. It is my belief that the same condition may cause the arteriosclerosis and the nephritis, as so called "renal retinitis" may be present in the absence of kidney lesions or marked arteriosclerosis, and albumen and casts may be found in so called "arteriosclerotic neuroretinitis." I have frequently found these conditions associated with focal infections, particularly where streptococci were found, and the teeth, tonsils and nasal sinuses were most frequently under suspicion. Optic atrophy may finally result, due to atrophy of the blood vessels and probably from the action of toxins on the retinal cells as well. Atrophy may also result from pressure of sclerosed intracranial arteries,—especially the internal carotid,—on the optic nerves or chiasm.

6. *Epidemic encephalitis*

Although paralysis of ocular nerves is common, involvement of the intraocular portion of the optic nerve is uncommon in epidemic encephalitis. Papilledema is rarely seen. It occurred in 4 of 168 cases studied by the Local Government Board (47) of London. The conclusion was reached that the optic nerve is involved when hemorrhagic infarction produces general cerebral hypertension. As an operation may be both useless and dangerous, a differential diagnosis should be made. I agree with Rosenberg (48) that in some cases this is by no means easy. We have never seen papilledema in epidemic encephalitis. Of 16 cases seen by us in the department of neurology of the Vanderbilt Clinic the optic nerve was involved in 3: neuritis of the intraocular portion of the nerve was present in 1 and retrobulbar neuritis in 2 cases. Holden (49) in the study of 100 consecutive cases noted blurring of the discs in 4 and papilledema in 1. He concludes that in most cases this complication is doubtless the result of increased intracranial pressure although in some instances it may be due directly to meningitis.

7. *Meningitis*

a. Acute tuberculous meningitis, probably on account of its tendency to affect the base of the brain, is frequently associated with optic neuritis, and Uhthoff (35) found tuberculous meningitis the cause of 1.1 per cent of his cases of papilledema. Choroidal tubercles were found by Swanzy (50) in 15 per cent of his cases of acute tuberculous meningitis and he considers the findings of great importance in differential diagnosis.

b. Cerebrospinal meningitis. Papilledema, according to some authors, is not commonly encountered. Barlow and Lees (51) saw it in 3 of 42 cases. From the hospitals and camps in the United States during the World War, de Schweinitz (52) collected reports of 11 cases of papilledema complicating meningitis. All of the cases were of the pneumococcic variety. Optic neuritis, neuro-retinitis, thrombosis of the central vein (Randolph (53)) and other signs of inflammation have been seen. Meningitis of otitic origin was accompanied by papilledema in 44 per cent of the cases observed by White (43) but in 50 per cent of cases of meningitis with increased spinal fluid pressure,

the ocular findings were normal. Streptococci were found in the cases with papilledema.

8. *Nephritis*

There has been much discussion in recent years regarding so-called albuminuric or renal retinitis, for the same retinal picture may be seen without nephritis, as in the cases observed by Noyes (54) and Haltenhoff (55), and it is well known also that nephritis may occur without retinitis. I believe that toxins, probably those derived from foci of infection, are frequently the cause of both nephritis and retinitis. Nephritis accounted for 1.1 per cent of all the cases of papilledema collected by Uhthoff. Provided the assumption is correct that a bacterial toxin or bacteria are frequently the cause of the retinitis, it is understandable that the papilledema closely simulates that of brain tumor or other conditions which cause increased intracranial pressure, for the toxins or the bacteria might possibly act to increase intracranial pressure. Papilledema of nephritis may be unaccompanied by hemorrhages or exudates but in papilledema of brain tumor even the star figures at the macula may be simulated, particularly in young subjects, although the figures are usually incomplete temporally. In the retinitis of nephritis, the exudates and hemorrhages are more frequently seen in the macular region, whereas they are generally close to the disc in increased intracranial pressure. Redslob (56) saw papilledema in a case of nephritis which strongly simulated a brain tumor. It is difficult, by the ophthalmoscopic examination to differentiate the nerve and retinal changes of increased intracranial pressure from those due to nephritis. The symptoms of headache and vomiting are frequently encountered in both conditions.

9. *Syphilis*

Cerebral syphilis was the cause of papilledema in 12 per cent of the cases collected by Uhthoff (35). In general paralysis, optic atrophy was found by Gudden (57) in 4.9 per cent of 1386 cases. Cerebrospinal syphilis may cause papilledema, raise cerebrospinal fluid pressure and in other ways simulate brain tumor, and as the Wassermann reaction may be negative in the ventricular fluid as well as the blood, it requires careful study to make a differential diagnosis. Spinal puncture is therefore indicated, but might be dangerous if a tumor is present. If a tumor is suspected, combined lumbar and ventricular

puncture seems to be a safe procedure, judging from the work of Smith and Hodgson (58).

10. *Lead poisoning*

Lead poisoning was the cause of papilledema in 0.3 per cent of the cases studied by Uhthoff (35), and although Jeaffreson (59) believes the nerve changes to be due to secondary vascular or renal disease, Oliver (60) has apparently shown to the satisfaction of de Schweinitz (61) that lead may act directly on the optic nerve. The inflammatory appearance of the swelling has impressed me in two patients in whom we have seen intraocular optic nerve involvement.

OTHER LESS FREQUENT CAUSES OF PAPILLEDEMA

a. Syringomyelia. Saxer (62) saw papilledema in one case of syringomyelia complicated by internal hydrocephalus.

b. Cranial trauma. Retinal hemorrhages are commonly noted but papilledema and atrophy are not seen as frequently as one would expect after cranial trauma without demonstrable injury to the bones but with hypertension of the cerebrospinal fluid. This may be due to the fact that patients with severe injuries frequently die before optic nerve changes have time to develop. I have found retinal diastolic pressure increased in brain injuries without fundus changes, and Kalt (5) and Magitot (63) in the absence of other ophthalmoscopic signs, have both diagnosed increased intracranial pressure by study of retinal diastolic pressure. Apparent optic atrophy following bilateral papilledema the result of cranial trauma is reported by Thorowgood, but in the patient visual acuity returned to normal. Krauss (64) operated on 218 patients with skull injuries. He noted papilledema in 10 and papillitis in 4 where the bones were uninjured, and papilledema in 14 and papillitis in 41 where the bones were injured. The dura was involved in all of the 41 cases of papillitis. I believe that all patients with brain injuries should be under the close observation of an ophthalmologist for at least ten days, as the ophthalmodynamometer and study of retinal blood pressures gives valuable data as to changes in intra-cranial pressure even though fundus changes may be absent.

c. Hydrocephalus. In congenital hydrocephalus optic atrophy is frequently seen, but perhaps owing to the possibility of separation of the sutures papilledema is seldom if ever encountered. Leber (65) has

seen a case of congenital, and Baxter possibly one of acquired hydrocephalus in which pressure symptoms were relieved after watery fluid,—which microscopically resembled cerebrospinal fluid, had escaped from the nostrils. These may have been cases of sinus disease. In acquired hydrocephalus, papilledema passing into optic atrophy is more commonly observed and may closely simulate brain tumor.

d. Lateral sinus infection. Optic nerve changes were found by White (66) in 40 per cent of his cases with lateral sinus infection.

THE DIAGNOSIS OF INCREASED INTRACRANIAL PRESSURE IN THE ABSENCE
OF PAPILLEDEMA THROUGH STUDY OF THE RETINAL BLOOD
PRESSURE

We are indebted to Bailliant (3) for a method of detecting intracranial hypertension in serous meningitis through study of the retinal blood pressure. In 1922, he apparently demonstrated the value of his method in the diagnosis of serous meningitis unaccompanied by fundus changes. Magitot (4), in 1926, diagnosed increased cerebrospinal fluid pressure in three cases of serous meningitis with negative ophthalmoscopic findings. Coppez (42) recently made an early diagnosis in a case of brain tumor through comparison of the retinal and humeral diastolic pressure. This entire subject has recently been made the object of a careful and complete study by Kalt (5), who has collected 13 observations where study of the retinal blood pressure indicated increased intracranial pressure in the absence of papilledema. His cases included serous meningitis, traumatic meningeal hemorrhage, intracranial complications of mastoiditis and otitis, and intracranial hypertension of unknown etiology without papilledema.

The relation of the retinal to the cerebral circulation

I agree with Bailliant (67) who said, "truly the retina is the image of the brain and the retinal circulation is the daughter of the cerebral circulation," for the retina is embryologically the direct extension of the forebrain, the retinal arteries are derived from cerebral arteries, and the veins return to the cranial cavity. The retinal arteries are similar to cerebral arteries in that they do not anastomose freely and that, under ordinary circumstances, they are under constant even pressure.

It is not strange then that the retinal arterial pressure should vary

with changes in the intracranial pressure which must influence cerebral arterial pressure. The exact mechanism of this process is still unknown.

Two theories may be advanced to explain the changes in the retinal blood pressure in increased intracranial pressure. The mechanical theory considers the cerebral arterial hypertension and the increased diastolic pressure in the retinal arteries which are branches of the cerebral arteries, a passive condition due to mechanical obstruction to the cerebral veins by the hypertension of the cerebrospinal fluid. The vasomotor theory views the hypertension as an active condition due to vasomotor influence. Neither theory adequately explains all the known facts, and the possibility of the endocrines particularly the suprarenal glands being concerned, is suggested to me by the work of Roger (68) in his study of cerebral blood pressure in animals. From our studies we learned that the increase of cerebral venous pressure by jugular compression is accompanied by an increase in the retinal diastolic pressure, *pari passu* with the rise of cerebrospinal fluid pressure. From the standpoint of vasomotor influence, Cushing has apparently shown that cerebral compression excites vasomotor impulses which raise arterial pressure sufficiently to maintain circulation in the arteries. Digital compression of the brain was shown by Bailliart and Hartmann to result almost immediately in increased diastolic pressure in the retinal arteries which subsided as soon as compression ceased. It has been experimentally demonstrated by Roger (68) in rabbits and dogs that the production of emboli in the cerebral vessels resulted in marked and prolonged rise in arterial blood pressure. He showed that acute rises in pressure could be produced but that the effect was not prolonged if the suprarenal glands were extirpated. Tournade (69, 70) has apparently shown that the centers of the brain contain a regulating mechanism for the cerebral circulation and that hypotension or hypertension in the cerebrospinal fluid immediately brings forth cardiac and vascular reactions which regulate the blood pressure. Teissier has found a local increase in the pressure of the temporal arteries in vertigo and inflammation of the brain. Adson (71) and Lillie, by means of a cannula in the lateral ventricle, noted marked fluctuations in pressure—880 to 980 mm. of water—with little or no change in the general blood pressure. From these and personal observations I am convinced that arterial hypertension is not always general and may be

localized in the brain and it is interesting to know that in many cases of glaucoma, where the intra-ocular pressure is raised and retinal diastolic, systolic, and venous pressure are very high, there is no abnormal increase in the brachial blood pressure.

METHOD OF DETERMINING THE BLOOD PRESSURE IN THE CENTRAL ARTERY OF THE RETINA

We are indebted to Bailliant (72, 73, 74) for a method of determining the blood pressure in the central artery of the retina, which seems to be of value for clinical studies, although the pressure found may not be the true pressure. Probably the only exact method, but one totally unadapted to clinical examinations is to insert a needle into the blood vessel as was done by Duke Elder (75) in a cat.

Bailliant's method in outline

1. Brachial blood pressure (sitting). Record systolic and diastolic readings.
2. Record intraocular pressure with Schiötz or Bailliant tonometer.
3. After conjunctival instillation of one drop of 1 per cent holocain, press foot plate of tested Bailliant ophthalmodynamometer against the sclera in the horizontal meridian in the angle of the outer canthus and make firm steady pressure against the eyeball towards its center. Note with ophthalmoscope first pulsation of retinal artery on the disc (diastolic retinal pressure in grams), continue pressure until arterial pulsation on disc ceases and the artery collapses, (systolic pressure in grams). Take average of three readings made at two minute intervals. Retinal pressure (grams) R. E. D.—S— L. E. D.—S—.
4. To determine the retinal arterial blood pressure in millimeters of mercury, refer to table XIV arranged by Magitot and Bailliant which considers the tension of the eyeball in mm. Hg. and the dynamometer pressure in grams; the ordinates give the result in mm. Hg. Local retinal pressure (mercury) R. E. D.—S— L. E. D.—S—.
5. Bailliant finds that the average retinal diastolic pressure varies from 30 to 40 mm. Hg and the systolic from 60 to 80 mm. Hg.

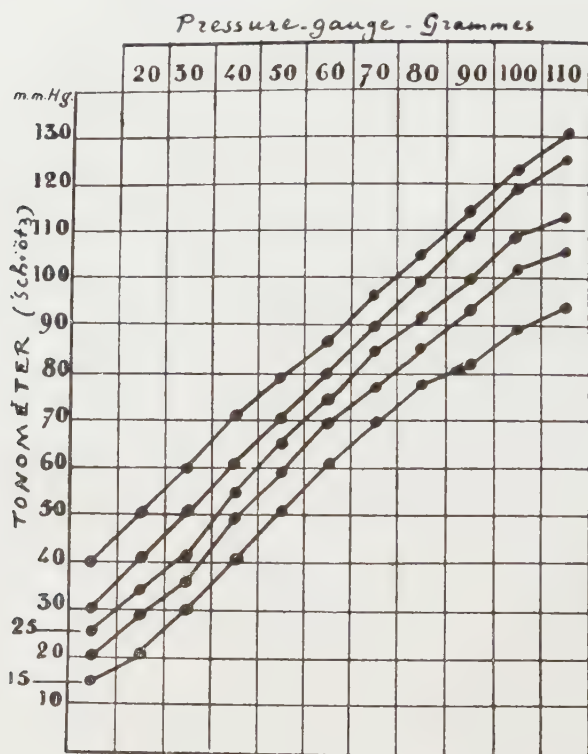
Table XV, which shows normal and pathologic formulae, we have found useful in studying the blood pressure of the retinal arteries.

The following study (table XVI) of the cerebrospinal fluid pressure as compared with the retinal diastolic and brachial pressure, made in the Department of Neurology, Columbia University, in conjunction with Dr. Leon H. Cornwall and with the assistance of Dr. H. T. Smith, has convinced me of the value of the Bailliant method, in certain cases, for the study of changes in the pressure of the cerebrospinal fluid and detection of increased intracranial pressure in the absence

of papilledema. I appreciate that any method of studying intraocular pressure which relies upon raising intraocular pressure through pressure on the eyeball involves inaccuracies, and this subject has been thoroughly investigated by Seidel (78, 79, 80, 81) and by Duke Elder (75, 82).

TABLE XIV

CHART ENABLING US TO ESTIMATE IN MILLIMETERS OF MERCURY THE PRESSURE EXERTED IN GRAMS ON THE EYE



In spite of inaccuracies inherent in the technic, I believe that a trained observer using tested instruments for a few months will then obtain valuable clinical data, particularly in the study of the same patient from day to day.

Summary of table XVI. In 6 patients a simultaneous study was

made of the diastolic pressure in the retinal and brachial arteries, and of the spinal fluid pressure recorded in millimeters of mercury before and after withdrawing a measured amount of spinal fluid. Five of the 6 patients had a disproportionate increase in the retinal diastolic pressure as compared with the brachial diastolic pressure.

TABLE XV

NORMAL AND PATHOLOGICAL FORMULAE OF RETINAL BLOOD PRESSURE
AS COMPARED WITH BRACHIAL BLOOD PRESSURE

*Arranged from data by Magitot**

NORMAL AND PATHOLOGICAL CONDITIONS AFFECTING RETINAL BLOOD PRESSURE		BRACHIAL BLOOD PRESSURE		RETINAL BLOOD PRESSURE	
		Dias- tolic	Sys- tolic	Diastolic	Systolic
Normal formulae	a. Normal brachial blood pressure	N	N	30 to 35 mm. Hg. is to brachial diastolic blood pressure as 0.45 is to 1	70 to 80 mm. Hg. is to brachial as 0.54 is to 1.
	b. High brachial blood pressure	H	H	Above normal and is $\frac{1}{2}$ brachial blood pressure as 0.50 to 1	Higher than normal
Increased intracranial pressure; choked disc, etc.		H	H	High	Normal
		N	N		
		L	L		
Angiosclerosis of the retinal arteries		H	H	Low	Low
		N	N		
		L	L		

Abbreviations used in table: H = High, N = Normal, L = Low, B/P = Blood Pressure.

* Magitot, A. P.: How to Know the Blood Pressure in the Vessels of the Retina. *Amer. Jour. of Ophthalm.* v, 1922.

All of these 5 showed increased intraspinal pressure with the mercurial manometer. The patient (case 1) with normal diastolic retinal and brachial pressure also had normal pressure of the spinal fluid. From these controlled studies of retinal blood pressure as compared with

TABLE XVI
COMPARISON OF THE PRESSURE IN THE RETINAL ARTERIES, BRACHIAL ARTERIES AND SPINAL FLUID

INITIALS, DATE, CASE NUMBER	HOSPITAL NUMBER OR OFFICE PATIENT	AGE, TIME OF EXAMINA- TION, OR SPINAL PUNCTURE	DIAGNOSIS	BRA- CHIAL BLOOD PRES- SURE SITTING		INTRAOCULAR TENSION BAL- LIART CORNEAL TONOMETER		RETINAL BLOOD PRESSURE		INITIAL PRESSURE SPINAL PUNCTURE; AMOUNT WITHDRAWN; REINJECTION PRESSURE	REMARKS
						R. E.	L. E.	R. E.	L. E.		
E. H. 4/4/27 Case 1	Vanderbilt Clinic Department of Neurology No. 45098	4:15 p.m.		111/65				4:20 p.m. before puncture		7-8 mm. Hg.; after withdrawing spinal fluid 4 mm. Hg.	Brain tumor? Optic atrophy
4/13/27				102/70		17	17	/32D	/34D		Slight headache following puncture
M. D. 4/4/27 Case 2	Vanderbilt Clinic Department of Neurology No. 43577	4:45 p.m.	Hemianopsia, brain tumor	165/75		19	19	/40D 4:50 p.m. /44 5:00 p.m. /40	/42D /50D	15 mm. Hg.; after withdrawal of 12 cc. Pressure 2 mm. Hg.; after inject- ing 25 cc. of Sal- varianized serum pressure 24 mm. Hg.	4/14/27. Has had headache since puncture; not influenced by posture. Refused re-examination
J. B. 4/20/27 Case 3	Vanderbilt Clinic Department of Neurology	61 4:35 p.m.	Neurosyphilis	132/64		18	17	130/50 4:50 p.m. 130/65	130/52 4:50 p.m. 130/58	9 mm. Hg.; after withdrawal of 12 cc. pressure 5 mm. Hg.	Cataract, hard to see vessels
4/27/27				118/64		14	14	71/37	71/37		No headache following puncture one week

A. S. 4/4/27 Case 4	Vanderbilt Clinic Department of Neurology No. 31659	4:20 p.m. spinal puncture	Tabs dorsalis	120/78	18	18	/70D	/70D	12 mm. Hg.; after fluid withdrawn pressure 4 mm. Hg.	Headaches second day after puncture, lasted 2 days, then felt well. Refused to be re- studied one week after punc- ture. Wasserman test, 4 +; cells, 50; colloidal gold, 54332100.
M. F. 5/1/27 Case 5	Vanderbilt Clinic Department of Neurology No. 34559	4:40 p.m. examination		118/78			/83D	/83D		
		42	Cerebrospinal syphilis	120/78	15	15	35/48	95/48	12 mm. Hg.; after 25 cc. withdrawn pressure 2 mm. Hg.	
		4:50 p.m.					92/55	85/62		
I. P. Case 6	Vanderbilt Clinic Department of Neurology	47		105/58	23	21	92/36		Slightly increased pressure; 24 cc. removed, 20 cc. Salvarsanized serum injected	
		4:30 p.m.					/46D			
		4:45 p.m.								
E. K. 3/17/27 Case 7	Vanderbilt Clinic Department of Neurology No. 45052	40	Papilledema	150/120	18	18	100/65	130/80		
A. B. 4/17/27 Case 8	Office	50	Optic atrophy	140/90	21	21	125/55	130/65	12 mm. Hg.; after 20 cc. withdrawn pressure 4 mm. Hg.	No headache or nausea following puncture

TABLE XVII
RETINAL BLOOD PRESSURE IN SUSPECTED INTRACRANIAL D SEASE

INITIALS, DATE, CASE NUMBER	HOSPITAL NUMBER OR OFFICE PATIENT	AGE, TIME OF EXAMINA- TION, OR SPINAL PUNCTURE	DIAGNOSIS	BRA- CHIAL BLOOD PRES- SURE, SITTING	INTRAOCULAR TENSION BAL- LIART CORNEAL TONOMETER		BLOOD PRESSURE OCULAR ARTERY		SPECIAL PROCEDURES	REMARKS
					R. E.	L. E.	R. E.	L. E.		
F. Y. D. 3/17/27 Case 1	C. B. office			135/120				/88D		Bilateral ethmoiditis, tumor of pons? Advanced angiosclerosis; hemorrhagic retinitis; chronic interstitial nephritis.
4/28/27				220/123	21	20		/120D		
5/4/27		6:00 p.m.		218/120				/81D	200 cc. 20 % glucose injected intra- venously	
		6:35 p.m.						/81D		No change in retinal diastolic pressure 30 minutes after glu- cose; patient died in second at- tack of pneumonia in 6 months
E. T. 1/26/27 Case 2	C. B. office	36	Papilledema Bilateral R. E. 3.5D L. E. 3D	118/82	17	17	87/37D	90/35D		Recurring attacks of blurred vision; no headaches; bilateral choked discs; question of brain tumor, but neurological exami- nation negative
3/26/27			3 1/2D O.U.	118/82	22	18	/45D	/60D		
3/31/27				108/78	17	20	/48D	/52D		
4/7/27				112/70	20	17	/60D	/57D		
4/14/27				116/70	19	19	/42D	/43D	25 cc. under pres- sure, not measured by manometer	

4/19/27					120/78	16	19	/52D	/50D		Headaches following puncture beginning to improve; attacks of blurred vision less frequent
4/28/27					114/80	21	20	65/55D	70/32D		No headaches
E. T. 1/26/27 Case 3	N. Y. Eye and Ear Infirmary No. 131			Purulent bilat- eral ethmoi- ditis. Bilateral papilledema R. E. 3.5D L. E. 3 D	118/82	17	17	85/38D	87/40D		Roentgenograms of head show chronic ethmoiditis; tempera- ture 104; pus in both ethmoids; patient died during radical eth- moid operation

brachial pressure and manometric studies of cerebrospinal fluid pressure, we were led to conclude that the ophthalmodynamometer of Bailliarl gave strongly suggestive evidence of the presence of increased intracranial pressure in the absence of papilledema, disease of the retinal arteries, and general arterial hypertension.

PRESSURE OF THE CEREBROSPINAL FLUID AFTER SPINAL PUNCTURE

In Kalt's (5) studies of the retinal blood pressure after spinal puncture, he noted a fall in pressure in 6 of the 8 cases, but Bailliarl found the pressure higher after spinal puncture. In cases 7, 5 and 6 in table XVI, the pressure in the retinal arteries was higher after spinal puncture than it was before, but in case 2 it was lower, although 25 cc. of salvarsanized serum were injected, and immediately following this injection the pressure of the spinal fluid was 24 mm. of mercury. This apparent discrepancy may be explained by a local increase of cerebrospinal fluid pressure. In case 6 the pressure was higher after spinal puncture and in this case 20 cc. of salvarsanized serum were injected. If the increased retinal diastolic pressure actually signifies increased intracranial pressure immediately following spinal puncture, might it not be due to rapid dilatation of the previously compressed cerebral vessels and rapid formation of cerebrospinal fluid? The rapid formation of the aqueous is observed after paracentesis. If the puncture wound remained open or there was marked sclerosis of the cerebral vessels or impairment of the secretory function, this might account for the fact that cerebrospinal fluid pressure is not raised in all cases following the puncture.

That a study of retinal blood pressures may also give valuable data as regards the effect of treatment on the pressure of the cerebrospinal fluid and on the progress of the condition, is suggested by table XVII.

Summary of table XVII. In cases 1 and 2 there was a pathological increase of diastolic pressure in the retinal arteries as compared with the brachial arteries, and brain tumor was suspected. Spinal puncture apparently caused a decrease in the pressure of the cerebrospinal fluid in case 2. Intravenous injection of a 20 per cent solution of glucose seemed to have had no immediate effect in lowering the retinal blood pressure in case 1 although the patient's vertigo was apparently improved by the injection.

Case 3 had bilateral papillitis of 3 diopters, but the retinal diastolic pressure was not elevated in comparison with the brachial diastolic

TABLE XVIII
PRESSURE IN THE RETINAL ARTERIES OF HUMAN BEINGS ACCORDING TO DIFFERENT INVESTIGATORS

INVESTIGATORS	METHOD	AGE OF SUBJECT	NORMAL DIASTOLIC IN MM. Hg			NORMAL SYSTOLIC IN MM. Hg			REMARKS
			Low	Mean	High	Low	Mean	High	
Baillart (67-77) Baurmann (83) Baurmann (83)	Baillart (74) Baillart (72) Physiologic estimation		30.0	35.0 52.0 60.0*	40.0	60.0	70.0	80.0	
Baurmann (83) Blüding (84)	Seidel (80) Intraocular pressure raised by air pressure	9-45	46.6 49.0	53.7 63.5	60.0 78.0	70.0 80.0	80.1 101.5	95.0 123.0	Estimation from known physiologic facts Pressure in central artery
Duverger and Barre (85)	Baillart (74)		50.0	55.0	60.0	80.0	90.0	100.0	
Gaudissart (86) Seidel (80)	Baillart (74) Seidel (80) sitting, no anesthesia of eye		30.0	30.0 37.5	45.0	70.0 100.0	75.0 110.0	80.0 120.0	Healthy, normal people, systolic blood pressure 100 to 120 mm.Hg
Average all authors			41.1	48.3	56.6	76.6	87.7	99.6	
Averages	Baillart method		40.0	43.0	50.0	70.0	78.3	86.6	
	Seidel method		38.3	45.6	52.5	85.0	95.0	107.5	

* Not less.

TABLE XIX
RETINAL ARTERIAL BLOOD PRESSURE IN DOGS

INVESTIGATORS	METHOD	DIASTOLIC MM. Hg	SYSTOLIC MM. Hg	REMARKS
Leplat (88)	Bailliant (74)	50-65	80-90	Retinal arteries observed
Lullies and Gul- kowitz (89)	Intraocular pressure raised and mano- metric control	50-70	92-108	
Weiss (90)	Raising intraocular pressure mano- metric control	50-70	80-100	
Average.....		50-68.3	84-99.3	

TABLE XX
NORMAL PRESSURE IN THE RETINAL ARTERIES IN SITTING POSITION
Assisted by Dr. Henry T. Smith

NAME OF PATIENT AND NUMBER	AGE	METHOD	GENERAL BLOOD PRESSURE		OCULAR TENSION		RETINAL BLOOD PRESSURE DIASTOLIC MM. Hg		RETINAL BLOOD PRESSURE SYSTOLIC MM. Hg	
			Sys- tolic	Dias- tolic	Bailliant Tonometer		R. E.	L. E.	R. E.	L. E.
					R. E.	L. E.				
1. A. H.	28	Bailliant	118	84	17	17	38	38	80	76
2. H. S.	20	Bailliant	114	80	20	18	45	38	88	78
3. M. K.	39	Bailliant	124	90	18	18	42	48	84	82
4. R. D.	24	Bailliant	110	60	16	16	30	25	58	55
5. E. S.	30	Bailliant	124	75	18	16	30	30	72	72
6. E. G.	31	Bailliant	130	86	17	17	32	34	70	72
7. B. S.	29	Bailliant	116	85	18	18	30	30	72	74
8. G. W. K.	34	Bailliant	126	78	16	18	34	38	68	74
9. W. E. S. G.	15	Bailliant	102	55	18	16	18	18	36	36
10. R. M. C.	32	Bailliant	114	70	17	17	25	25	58	58
11. T. P. C.	30	Bailliant	124	80	18	18	30	30	64	64
Low	15	Bailliant in each case	102	55	16	16	18	18	36	36
High	39		130	90	20	18	45	48	88	82
Average.....	28.4		118	76	17.5	17	32.2	32.2	68.2	67.4

TABLE XXI

EFFECT OF JUGULAR COMPRESSION AND POSTURE ON RETINAL BLOOD PRESSURE

INITIALS, AGE, DATE, HOSPITAL NUMBER	DIAGNOSIS	TIME	BRACHIAL BLOOD PRESSURE LYING		INTRA- OCULAR PRES- SURE BAIL- LIART LYING		BLOOD PRESSURE CENTRAL ARTERY RETINAL, LYING		SPINAL FLUID PRES- SURE MM. Hg, LYING ON SIDE	REMARKS
			Sys- tolic	Diast- tolic	R. E.	L. E.	R. E.	L. E.		
U. C. 39 10/27/27 Vanderbilt Clinic, Depart- ment of Neurol- ogy	Cerebro- spinal sy- philis	<i>p.m.</i>								
		5:00	112	65	17	17	83/43	83/43		Before punc- ture pa- tient sit- ting
		5:10					/63			Lying prior to insert- ing spinal puncture needle
		5:15					/65		20	After insert- ing needle
		5:25					/80+		70	Jugular compression 15 seconds
		5:27					/90		75	Jugular compression 15 seconds
		5:28							8	Removal 25 cc. of spinal fluid
		5:30							6	Removal 30 cc.
		5:32							4	Removal 35 cc.
		5:36					/65			After with- drawal of spinal puncture needle

pressure. At operation on the ethmoids pus was found; the patient subsequently died. When papilledema has developed, as Kalt (5) has remarked, one-third of the cases shows normal blood pressure in the retinal arteries, and in many others the pressure is only slightly elevated. I have been able to confirm Kalt's observation that some patients with papilledema show variations of the pressure in the retinal arteries. Case 2, table XVII is an example of this. In cases 2 and 3 there was low blood pressure in the retinal arteries when the papilledema was well established.

WHAT IS THE AVERAGE PRESSURE IN THE ARTERIES OF THE RETINA OF HEALTHY SUBJECTS?

Although Seidel (81) states that Bailliart's and similar methods of determining retinal blood pressure are inaccurate, it is interesting to note in table XVIII that the averages of several authors using Seidel's and Bailliart's methods are approximately the same for the diastolic pressure, although the systolic readings are higher with Seidel's, as they are when Seidel's own findings are compared with Bailliart's.

All the authors using Seidel's (80) method except Bliedung (84) obtained higher diastolic findings than Baurmann (83) estimated they should be, from his knowledge of the physiology of blood pressure. Duke Elder (75-82) believes that the Bailliart method measures the lateral blood pressure in the ophthalmic artery and that Seidel's method of studying the pressure in the anterior ciliary arteries by applying a small pressure chamber over them does not indicate the true retinal blood pressure. By means of special technic Duke Elder (75) connected the retinal arteries of a cat with a manometer and found the pressure 88.5/64 mm. Hg. In studying the blood pressure in the retinal arteries of cats as compared with the blood pressure in the arteries of the iris, Magitot (87) and Bailliart found that in normal eyes these pressures are practically identical, and in the cat 45 is the average normal diastolic pressure and 100 the average normal systolic pressure, but the latter varies markedly with the general blood pressure.

The findings of several authors gave the average diastolic pressure of dogs (see table XIX) as 60 which is the figure Baurmann (83) believes more nearly represents the true retinal diastolic pressure in man. Our own studies of the retinal blood pressure of humans, made with the assistance of Dr. H. T. Smith, are summarized in table XX.

Summary of table XX. Eleven patients between the ages of 15 and 39 years, with an average age of 28.4 years were examined in the sitting position by the Bailliart method to determine the systolic and diastolic pressure in the retinal arteries. Their brachial blood pressure averaged 118/76 mm. Hg. Their intraocular tension as studied by the Bailliart corneal tonometer averaged 17.5 in the right eye and 17 in the left. The retinal pressure averaged, in the right eye 68.2/32.2 and in the left eye 67.4/32.2 mm. Hg.

These figures are lower than the figures obtained by other observers but this was a group of young healthy adults chosen at random with no serious eye defects although two complained of headache. These cases were studied after I had had a years experience in the use of the Bailliart method and at first my readings were much higher and I believe less accurate. In order to determine the effect of posture and jugular compression on retinal blood pressure several patients were studied while standing, sitting and lying, and with the spinal puncture needle inserted, when jugular compression was made. A fairly typical reaction is recorded in table XXI. It may be seen from the data recorded in table XXI that retinal diastolic pressure increases when the patient lies down although in the patients examined, the brachial diastolic pressure has been lower. Jugular compression in the four patients so far studied has always been accompanied by a marked rise in the pressure of the cerebrospinal fluid and a marked and apparently immediate increase in the diastolic pressure in the retinal arteries. The diastolic pressure in the central retinal arteries of eight patients, examined by the Bailliart method, averaged 35 mm. Hg. standing, and 41 mm. Hg. lying; in all but one case, in which there was no apparent change in the pressure, the figures were higher while the patient reclined.

CONCLUSIONS

1. Fundus changes, if properly interpreted, may give valuable information in suspected increased intracranial pressure, but negative findings unless the retinal blood pressure is also known should not be considered of too great importance.

2. In spite of inaccuracies and difficulties inherent in Bailliart's technic for determining the diastolic and systolic blood pressure in the central artery of the retina, I believe that a trained observer, using tested instruments for a few months, will obtain valuable clinical

cal data in patients in whom increased intracranial pressure is suspected.

3. The average diastolic and systolic pressure in the intraocular arteries as given by authors using several different technics is 48.3 diastolic and 87.7 mm. Hg. systolic. The average of several authors using Bailliart's method is 43 diastolic and 78.3 mm. Hg. systolic, with Seidel's method 45.6 diastolic and 95 mm. Hg. systolic. As in practically all instances the blood pressure, the position of the patient and the age of the patient are not recorded these figures are difficult to compare with ours. Our findings in the sitting position in eleven patients between the ages of 15 and 39 years averaging 28.4 years, whose blood pressure averaged 118/76 mm. Hg. and intraocular pressure with the Bailliart tonometer averaged 17 in the right eye and 17.5 mm. Hg. in the left eye, the retinal blood pressure in the central artery of the retina averaged 68.2/32.2 in the right eye and 67.4/32.2 mm. Hg. in the left eye.

4. Several patients were examined to determine the influence of posture on the retinal blood pressure. There was a marked increase in retinal diastolic pressure as the patient changed from the standing to the lying position, although brachial diastolic pressure decreased.

5. Jugular compression caused a marked increase in the cerebrospinal fluid pressure, which was accompanied by a marked rise in the diastolic pressure in the retinal arteries in four patients examined.

6. From experimental and clinical data obtained with Bailliart's ophthalmodynamometer, it may be said that in the absence of papilloedema, disease of the retinal arteries and general arterial hypertension, a diastolic blood pressure in the central artery of the retina greater by 10 or 15 mm. Hg. than one half the brachial diastolic blood pressure when the patient is sitting or standing, strongly suggests increased pressure in the cerebral arteries, the result of increased intracranial pressure. The exact mechanism which produces this phenomenon is not definitely determined.

7. When papilledema is established the retinal blood pressure findings may be so misleading as to indicate a low intracranial pressure in some cases where it is actually high. No explanation is offered for this phenomenon.

8. Repeated studies of the blood pressure in the central artery of the retina are of value for the early diagnosis of increased intracranial pressure in the absence of papilledema, and when the diagnosis is established, for noting augmentation of pressure and remissions.

9. Spinal puncture is conceded to be dangerous if a brain tumor is present, and combined lumbar and ventricular puncture or puncture of the lateral ventricles is a major surgical operation. Therefore if a brain tumor is suspected, study of the retinal blood pressure is apparently of practical value for determining the presence or absence of increased intracranial pressure, and for noting changes of pressure in the absence of papilledema.

10. Papilledema is frequently a late rather than an early sign of increased intracranial pressure and may be absent in the presence of long continued hypertension.

11. No important diagnostic conclusions can usually be made even though papilledema is unilateral or there is disproportionate swelling of the nerve heads in brain tumor cases; but in brain abscess the lesion early in the disease is frequently on the side of the papilledema or on the side of the greater degree of edema of the optic nerve. The fact that early in a case of brain abscess the edema of the optic nerve is greater on one side is merely suggestive of ipsilateral localization, if the intraocular tension is equal in both eyes or greater in the eye with the more pronounced swelling of the nerve.

12. From the standpoint of pathology, simple edema seems to be the most important single factor in the production of the microscopic and ophthalmoscopic picture of papilledema in brain tumor, meningitis and the so called "Retinitis of Nephritis."

13. From clinical, pathological and experimental studies of the pathogenesis of papilledema, mechanical blocking of lymphatic drainage by pressure of the cerebrospinal fluid on the optic nerve, and lymphatic channels surrounding the central artery of the retina seems to be the most important factor in producing edema of the disc. If the increase of cerebrospinal pressure is sudden, especially when inflammation is present, the lymphatics tend to be obstructed early. In the chronic cases, the pressure may rise so gradually that lymphatic drainage is not greatly disturbed until blocking occurs either from pressure atrophy or from low grade inflammation. Mechanical obstruction to venous outflow is undoubtedly present and is possibly a factor in the production of hemorrhages and exudates but is probably a less important factor in the edema than lymph stasis.

I acknowledge with gratitude the enthusiastic coöperation of Dr. Leon H. Cornwall and Dr. Henry T. Smith in the studies of the retinal blood pressure, and Edgar B. Burchell in the preparation of pathologi-

cal specimens. I am indebted to Dr. George E. de Schweinitz, Dr. Wilder Penfield, Dr. Louis Casamajor, Dr. J. E. Sweet and Dr. Wm. V. Cone for their constructive criticism and many valuable suggestions in conducting investigations and in the preparation of the manuscript.

DISCUSSION

The following question submitted to Dr. Berens before the Commission, together with the answer to it, is here reported verbatim.

DR. WOLFF: Since intraocular and cerebrospinal fluid pressures are so closely related to pressure changes in the jugular vein, can one waive the venous pressure alterations within the eye which must result from pressures on the eyeball? Slight displacement is also inevitable. In other words, can one ignore the intraocular pressure increase and the kinking of retrobulbar veins which must follow when pressure is applied to the eyeball? Do you not temporarily raise the intraocular pressure in this way?

DR. BERENS: Dr. Wolff has emphasized an important point. That is one of the inherent difficulties in Bailliart's method of determining the pressure. Undoubtedly as we press upon the eyeball we do press upon the venous outflow, and we raise tension in that way. With this method used in a number of cases, simultaneously making spinal fluid examinations, we have found that we actually may determine, before we insert the spinal puncture needle, that there will be an increased intracranial pressure. Apparently therefore, the method is sufficiently accurate as a practical clinical test. As an absolute indicator of the true diastolic pressure in the retinal arteries it is not accurate. The only way this may possibly be determined accurately is by the method suggested by Duke Elder of inserting a needle directly into the retinal artery. This has been done in the cat but is not applicable clinically.

With the Seidel method which we have demonstrated, Seidel says he avoids kinking of the veins and also kinking of the arteries. A few investigators believe that one may more accurately determine the true retinal blood pressure by the Seidel method but the entire subject requires further study and does not affect the apparent fact that the Bailliart method which is simpler, when used in the same patient from day to day seems to give valuable clinical data.

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CHAPTER XX

VISUAL FIELD DEFECTS DUE TO INCREASED INTRACRANIAL PRESSURE

G. E. DE SCHWEINITZ, M.D.

THIS communication concerns itself, briefly, (a) with certain changes in the visual field which interpret pathologic alterations in the optic papilla (nerve-head), when such alterations are mainly due to increased intracranial pressure; (b) with certain anomalies of the disposition of the visual field, that is, the relative position of its parts, which from time to time have been ascribed to increased intracranial pressure.

The subject matter is necessarily thus limited, and reference, except incidentally, to the various field defects created by interference with the functions of the visual pathway from the chiasm to the occipital cortex is omitted because, in these circumstances, it is the pressure of the lesion or condition, tumor or otherwise, and not the rise of pressure in the cerebro-spinal fluid with which it is associated that causes the field deformations.

I. PAPILLEDEMA (CHOKED DISC) AND THE VISUAL FIELD

Papilledema (using the Elschnig-Parson's term in place of "choked disc") is most frequently due to increased intracranial pressure. Traquair (1), in order to define exactly such edema of the nerve-head, and to distinguish it from a similar papilledema of other origin, for instance, a local optic nerve lesion, suggests the name "plerocephalic edema."

Normally, a continuous extension exists between the general subdural space and that of the optic nerve. Hence, elevation in the pressure of the cerebrospinal fluid in the former is transferred to the latter, where its compressive action is chiefly exerted on the central retinal vein and on the lymphatics of the optic nerve which pass out in its walls. Consequently venous engorgement and lymph stasis take place, and the intraocular pressure being normal, disc-edema

results. This is the usual explanation, but almost certainly is not the whole story.

The conspicuous visual field defect caused by papilledema thus established is the so-called "enlargement of the blind spot," or that oval area of blindness which corresponds to the entrance of the optic nerve, which area is surrounded by a relative zone of amblyopia for white, about 1 degree in width. This is "the pericecal amblyopic zone." It is around this zone and continuous with it that "the enlargement" takes place, and is therefore properly denominated "pericecal scotoma."

It has been stated that antedating the ophthalmoscopic signs which indicate very early papilledema—blurring of the upper and lower disc edges, or of the upper nasal quadrant, and gradually extending along the nasal margin—there may be a period which has been called "the imminence of edema," characterized by distention of one (or two) divisions of the retinal veins, which are unevenly tortuous.

This dilatation is ascribed to pressure upon the vein in the inter-vaginal space at a point where at the height of the choking, Dupuy-Dutemps maintains this flattening of the vein reaches its maximum.

Twice I have seen this phenomenon. But Mr. Leslie Paton, whose large experience and expert observation command attention, is unable to persuade himself that such a venous congestion precedes blurring of the disc margins.

Whether at this stage perimetry would reveal an enlarged blind spot, that is, a pericecal scotoma, is uncertain, or at least, observations have been too infrequent and too imperfect to permit an affirmative answer, and none has been made, in so far as I am aware, since modern field-testing technic has been introduced. More studies in this respect are required.

Whether a change in the size of the "blind spot," particularly in a vertical direction, analogous to that reported by Ramsay and Sutherland as an early sign of "congestion of the disc" in sympathetic ophthalmia, attributed by them to turgescence of the superior and inferior branches of the retinal vessels, is present as a sign of early papilledema due to increased intracranial pressure, or as an indication of vascular congestion when the disc is not yet blurred, is open to doubt.

Certainly in some investigations by Holloway and myself (2), when, however, the earliest stage of papilledema was present, such alterations were never found.

As is well known, enlargement of the blind spot may sometimes be demonstrated in cases of posterior accessory sinus disease, even prior to the development of a central scotoma, and at a period when disturbance of vision is not yet apparent. This is the so-called "Van der Hoeve (3) sign," which its discoverer attributes to early involvement of the peripapillary bundle.

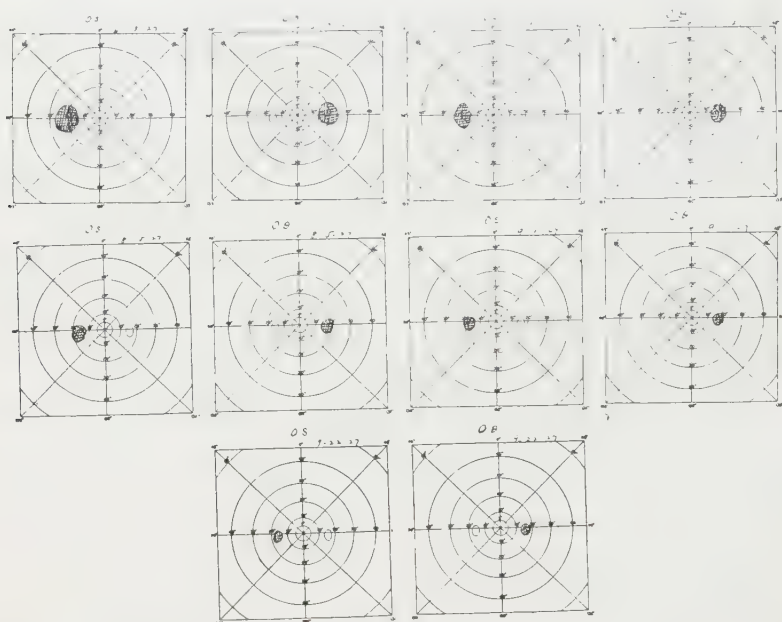


FIG. 98. Gradually diminishing enlargement of the blind spot in a case of choked disc, + 6D. right, + 7D. left. Spinal pressure originally 40 mm., gradually diminishing, but never falling below 20. Direct vision normal throughout the period from 6.13.27 to 9.22.27. Treatment repeated lumbar punctures. Vision $\frac{6}{8}$ throughout the period.

This suggests that it is possible that a similar enlargement of the blind spot may be present prior to the earliest nerve-head change indicative of choked disc, and I am quoted by Traquair (4) as having made this observation, which his experience does not confirm, as he has always found the fields normal until swelling of the papilla is definite. This confessedly is apparently as it should be, for as this author points out, the pericecal scotoma, that is, enlargement of the

blind spot, to use the ordinary term, depends upon increasing thickness and opacity of the nerve-fiber layer immediately around the optic disc, and upon pushing away of the retina from the edge of the porus opticus, whereby the area devoid of percipient elements becomes increased. It is difficult, but not impossible, to believe that blind spot enlargement could be demonstrated prior to the ophthalmoscopic evidence of its existence.

However, if I have made this statement, I am unable to trace the exact reference, but be that as it may, I certainly often have urged a careful investigation of the "blind spot area," in cases of suspected lesion capable of elevating intracranial pressure at a period when early disc edema is often not present. And this period may be of considerable duration, because it is well known, as Elsberg and others have pointed out, that papilledema is often a late rather than an early sign of brain tumor. In other words, as I have stated elsewhere, "the intracranial neoplasm must have existed for some time and the increased intracranial pressure must have lasted for a definite period before engorgement-edema develops."

Now although in the light of the accepted anatomical reasons for "enlargement of the blind spot," and according to the statement of one of our most accomplished visual field experts, just quoted, increase of the pericecal scotoma does not take place at this period (and Traquair must have studied the blind spot area at this time, otherwise he would not have written the sentence which has been recorded), I regard it as a field of research not to be neglected.¹

Another point is this: Walter Parker's (6) experimental studies have demonstrated that papilledema due to increased intracranial tension appears first in the eye with the lesser intraocular tension. If this is true in human beings, enlargement of the blind spot ought to appear first in the eye with the lower tension. The research, therefore, should include ophthalmoscopy, perimetry and tonometry.

Finally, it is well known that elevated intracranial pressure by no means always causes papilledema, for instance, in the hydrocephalus of children. Moreover, in 15 to 20 per cent of brain tumors, choked disc either does not appear at all, or only a few days before a

¹ Luther Peter, whose blind spot studies are well known (5), informs me that he does not recall that he has observed this phenomenon, but I infer that he also does not regard it as one that careful examination might not reveal.

fatal issue supervenes. Systematic studies of the blind spot area in these cases appears to be lacking.

With the appearance of definite ophthalmoscopic signs of papilledema the result of increased intracranial pressure, the pericecal amblyopic zone begins to enlarge, and sometimes slowly, sometimes rapidly, a scotoma is formed around the blind spot, and extends toward the fixing point.

Naturally, the "intensity" of the scotoma diminishes toward its periphery, where it joins the unaffected field, and the size of the "defect" corresponds with the degree of disc swelling.

When a scotoma is thus formed, that is, the so-called enlargement of the blind spot, it may be regarded as its pathologic norm. But sometimes the scotoma is not merely a somewhat oval sloping defect, but may exhibit pointed extensions from the main "blind area" which can be charted due to variations in the disposition of the engorgement process or in the thickening of the nerve-fiber layer around the disc. The extensions now referred to differ entirely "from the prolongations of the amblyopic zone . . . which represent the projections of the larger retinal vessels near the optic disc," which have been so elaborately studied by J. N. Evans (7) in our country.

Ophthalmoscopically, papilledema due to increased intracranial tension and that due to optic nerve involvement are often difficult, if not impossible, to differentiate. Hence the importance of the direct visual test, because in the former, if uncomplicated, that is, if atrophy and macular disorder are absent, corrected sight is normal and remains so for a long time, while in the latter, from its earliest stage direct vision is almost always involved.

Satisfied that the papilledema is due to increased intracranial tension, the ophthalmologist must answer the neurologist's oft repeated question as to how long it is safe to wait before resorting to operation, which as a sight-saving procedure must be done early.

Perimetry now supplements the ophthalmoscope, and daily measurements of the blind spot are essential, associated with frequent quantitative peripheral field tests, for it is in the periphery and intermediate zones that the first depression due to beginning atrophy takes place.

Should in any case of papilledema due to increased intracranial tension, the corrected central vision having been normal, signs of its depreciation appear, a decision should be quickly reached as to whether

this fall in visual acuteness is due to beginning atrophy of the nerve or to a beginning macular change.

Again perimetry becomes important, for if it is the latter due to the spreading of edema to the macula, in the center of the field a scotoma will be found, that is, one characterized by relative blue blindness which indicates early involvement of the outer retinal layers, followed, it may be, by a paracentral relative scotoma for blue.

But if atrophy is beginning, the peripheral field, properly tested, will show depression, and macular edema being absent, the relative blue scotoma of distinctive features will not obtain. Naturally, if the "macular fan" is present, it can be seen with the ophthalmoscope, but I refer now to a macula which is apparently unaffected, I say "apparently," but remember that centric ophthalmoscopy and red-free light ophthalmoscopy may reveal what ordinary ophthalmoscopy fails to demonstrate.

Decision as to early operative procedures does not, of course, depend only on visual field examinations associated with tests of the direct vision. For instance, repeated attacks of temporary amaurosis, due to intermittent pressure on the chiasm from a distended third ventricle indicating increasing intracranial pressure, may be one of the indications for operation even in the absence of papilledema. In other words, as Paton has said, it is not necessarily on the first development of papilledema, but on the first signs of visual failure that palliative trephining is indicated if sight is to be saved.²

II. INTERLACING AND INVERSION OF THE COLOR LINES OF THE VISUAL FIELD IN ASSOCIATION WITH INCREASED INTRACRANIAL TENSION

The theme for discussion named in the subtitle is one which requires an excursion into past history and the temporary resurrection of a settled subject, and therefore it would seem might well be omitted. But for reasons which shall presently appear it is desirable on this occasion and in this audience to make a brief reference to this topic.

² It is not germane to the present topic to discuss Baillairet's method of determining the blood pressure in the retinal artery and its relation to increased pressure in the cerebral arteries, the result of elevated intracranial pressure. This has been well taken care of by Dr. Berens. Eagleton's observations, quoted by Osnato and Giliberti (8) on "unoutspoken vestibular manifestations of increased intracranial pressure" are also not relevant in this discussion.

Long ago Charcot (9) announced that functional visual field defects ascribed to hysteria, that is, concentric contractions, reversal of the color fields, or interlacing of their boundaries, etc., were also demonstrable in association with organic conditions, for instance, lesions of the posterior part of the internal capsule and brain tumor, and therefore also with increased intracranial tension.

In 1902, independently of these observations, Cushing's attention was attracted to this subject, and seven years later, in association with Bordley (10), he put on record the results of the first painstaking and elaborate study in this respect.

Their data were derived from 56 cases of brain tumor, and utilizing pure spectral colors, they found interlacing color lines as the predominant field defect 25 times, color inversion 9 times, but no color changes



FIG. 99. Œdema of disc from increased intracranial pressure. Objects $\frac{3}{2} \frac{0}{0} \frac{0}{0}$, $\frac{1}{2} \frac{0}{0} \frac{0}{0}$. 1924, July 25th, October 12th, and November 9th, from a case of brain tumor. Vision $\frac{6}{6}$ throughout.

9 times. In four cases with color interlacing but no choked disc, a tumor was found at operation. In 40 out of 42 cases after operation (palliative or radical) the color lines were restored to their normal relative functions.

They concluded that dyschromatopsia seemed to depend in some fashion on increased intracranial tension, the relief of which usually caused its subsidence, and it was possible that it might characterize organic lesions other than tumors of the brain.

Confirmation of these observations came from various observers and clinics, and two years later Bordley (11) reiterated his belief in the value of these color line inversions as a symptom of brain tumor.

In the same year, Cushing and Heuer (12), discussing dyschromatopsia in relation to the changes of choked disc, reported out of 123 cases of brain tumor that 53 showed simple color interlacing, or inver-

sion, and stated that these distortions of the color boundaries promised to be of some service "in making a more precocious diagnosis of increased intracranial tension than is commonly ventured on."

Earlier in the same year (13), in a paper with respect to the relief of the ocular manifestations of increased intracranial tension by cerebral decompression, based on examinations in the Frazier Clinic in the University of Pennsylvania Hospital, and referring to Cushing and Bordley's work, I made similar observations in a number of cases, but expressed the opinion that there was no justification in depending on this sign alone as one for recommending a palliative operation.

As the methods of field-testing improved, and the necessity of quantitative perimetry, screen and campimeter work became more and more evident, it was realized (and by no one more keenly than by Cushing) that the subject of dyschromatopsia as a sign of increased intracranial pressure must be reviewed.

With fine liberality, he turned over his entire material to Clifford B. Walker, and there followed his (Walker's) well-known thesis entitled "Color Interlacing and Perimetry" (14).

Time does not permit, nor is it necessary, a description of the modern and scientific perimetric technic employed. Suffice it to say that Walker definitely demonstrated that color interlacing and inversion are not reliable indications of increased intracranial pressure, and that most of the color interlacings found in the past in brain tumor cases may be accounted for by "various variables," largely psychologic and physical. Dr. Cushing at an early opportunity published a modification of his former views, and withdrew his previous endorsement of dyschromatopsia as a trustworthy index of increased intracranial pressure.

In spite of the "evidence in the case," summarized in the preceding paragraphs, physicians are not lacking who still cling to the belief that dyschromatopsias of the types described are reliable signs of increased intracranial tension, and from time to time I receive or see letters asking for information on this subject.

In a recent report from a well-equipped clinic to a physician with respect to the examination of his patient, this statement occurs: "You will notice on the enclosed chart the interlacing of the red and green fields, more or less characteristic of a basal lesion."³ Subsequent

³ The measurements were taken on the Lloyd stereo-campimeter.

fields, mapped with a graded series of test-objects failed to reveal any distortion of the color lines, or, in fact, any important abnormality.

There is no intention to dispute the diagnosis in this case (the studies are not complete), or to deny that various forms of dyschromatopsia are found in suggestible patients; also when a functional element is associated, as is often the case, with an organic lesion, but only to reiterate that such field deformations should not be regarded as trustworthy signs of increased intracranial tension, and to urge an avoidance of an "inadequate demonstration of the characters of the defects" (Traquair), by conscientious recourse to the quantitative methods of field-testing.

III. OTHER CONDITIONS ASSOCIATED WITH INCREASED INTRACRANIAL PRESSURE

Papilledema with distinctive ophthalmoscopic features due to increased intracranial pressure is certainly most frequently encountered in association with brain tumor, frequently with brain abscess, and also in some forms of cerebral lues independently of gumma or meningitis.

Ordinarily in the four varieties of meningitis, the nerve-head changes are those of papillitis (optic neuritis, descending neuritis), but occasionally a distinctive papilledema of the kind just referred to develops, for instance, in epidemic cerebrospinal meningitis with distention of the third ventricle, in epidemic encephalitis (I have seen three typical cases), in sinusitis (spheno-ethmoid infection, then unilateral), in hydrocephalus, in cerebral aneurism when this acts like a tumor and intracranial pressure is raised, in anemia (probably due to sinus thrombosis), in cranial injury, etc.

While there may be in such varied circumstances field defects indicating pressure on definite nerve tracts, there is nothing in the character of "the enlarged blind spot (pericecal scotoma) which connects it etiologically with one or other of the conditions named; it simply probably develops as the result of the transfer of the elevated pressure of the cerebrospinal fluid in the general subdural space to that of the optic nerve.

It is probable that the character of the pericecal scotoma (enlarged blind spot) caused by papillitis, which is due, for instance, to meningitis or a toxic process, differs in extent from one that is due alone to increased intracranial tension, that is, a papilledema, but it may be questioned if this would suffice to make a differential diagnosis.

which must depend largely upon ophthalmoscopic examinations and slit-lamp investigation (Köppe's sign).

There is no doubt, however, that true spurious optic neuritis (hyperopic disc) and early papilledema or papillitis may be distinguished by blind-spot-area investigation, as in the first instance a pericecal scotoma does not develop.

It has been suggested that the papillo-retinitis of Bright's disease may be due to cerebral edema, being, as it were, a modified choked disc (15).

This is certain, and it is important to emphasize it, that instead of the usual retinitis of chronic interstitial or glomerular nephritis, the *only* fundus lesion may be a typical papilledema quite indistinguishable from one that is caused by brain tumor. Foster Moore (12) reports two cases. I have also seen two cases, confirmed by autopsy, and I agree with him and with Ballantyne, whom he quotes, that the vital prognosis is especially grave in these circumstances.

Blind-spot studies alone would not suffice as a method of differential diagnosis, inasmuch as there are no distinctive features, in so far as I know, with respect to the one as compared with the other.

Whether the relative blue-blindness in the macular area as an early sign of renal retinitis, or the blue-blindness which, according to Gerhardt, may be a sign of the retinitis of chronic Bright's disease, are demonstrable in these circumstances I do not know. Such tests were not made in the cases I observed.

It is interesting in this connection to recall that Bordley and Cushing included "blue blindness" and "islands of blue blindness" among the dyschromatopsias which they at one time thought might indicate increased intracranial tension.

Cerebral trauma, associated as it is with acute rise in intracranial pressure, is a frequent cause of rapid papilledema, and the swelling of the papilla is apt to appear soon after the cranial injury. These disc edemas occur in simple concussion or brain contusion, furrow wounds, fractures or penetrating wounds, and both with and without epi- or subdural hemorrhage.

They and their characters furnish indications for operation, and the need of frequent ophthalmoscopic examination is evident.

Often, however, the value of blind-spot studies in these cases, as previously described in the papilledema of brain tumor, cannot be utilized owing to the patient's mental condition.

In a certain number of the cases the disc-edema disappears without operative release of intracranial tension.

Bilateral papilledema arising weeks or months after a cranial injury is a sign of grave significance, indicating a serious intracranial lesion which had in its earlier existence escaped attention.

The opportunities of studying the effects of injuries of the brain on the visual field were most elaborate during the Great War, especially those which pertained to the cortical centers of vision and the optic radiations by Sir Gordon Holmes, Sir William Lister and M. L. Hine in England, and H. W. Scarlett and S. D. Ingham in the United States. But their portrayal does not belong to the present topic.

Manifestly, in the early stage of pure concussion of the brain (if that term is permissible), that is, to use Trotter's language, "an essentially transient state due to head injury . . . which does not as such comprise any evidence of structural cerebral injury," visual field studies are impossible.

Even in the period of post-concussion neurosis, which Osnato and Giliberti (16) regard as a traumatic encephalitis, accurate charting of the visual field is often difficult. Positive scotomas have been noticed, which could not be "confirmed objectively." The authors quoted found the visual fields of those thus affected to be normal, except in the presence of organic lesions of the eyes. Their tests were made a considerable time after the original injury, and their methods are not described; but they recognized the importance of Hine's observations that the test-objects, both white and colored, must be of small size; otherwise a partially recovered lesion may be missed and the field found full.

Some observations of my own, especially recently in a case of pronounced post-concussion neurosis failed to detect any depression of the visual field, either in the central or peripheral zones, but the tests were performed in unfavorable circumstances.

The temporary hemianopsias and scintillating scotomas of migraine are due to angiospasm, and not to the increased intracranial pressure which may be present.

The moderate depression of the fields exhibited by patients with cerebral arteriosclerosis, and by the subjects of chronic headache, as they were grouped by Weir Mitchell, are probably due, to quote Traquair, to "impaired cerebation depending on physical enfeeblement."

In summary, it may be said: Increased intracranial pressure apparently produces no field defects which may be regarded as distinc-

tive, save only that the papilledema for which it is probably mainly responsible is interpreted in the field by a pericecal scotoma, ordinarily known as "enlargement of the blind spot."

But increased intracranial pressure may exist for a long time without causing papilledema. There is, however, no satisfactory proof that this "enlargement" has been demonstrated prior to ophthalmoscopically evident edema, that is, blurring of the nerve-head margins, due partly "to the increasing depth of the tissues of the papilla." Nevertheless, it is possible that the binocular Gullstrand ophthalmoscope would reveal changes in this period not detectable by the ordinary ophthalmoscope. Additional perimetric observations are desirable.

A developed papilledema and the character and extent of the blind spot enlargement which it produces do not indicate the position of the tumor which has caused the rise of intraocular pressure upon which they depend. However, tumors of the cerebellum are prone to cause a more intense form of papilledema, and consequently a greater size of the pericecal scotoma than cerebral neoplasms, and the same is probably true of morbid growths of the mid-brain and the thalamus, while the edema is less pronounced in subcortical, parietal and frontal lobe tumors.

Perimetric studies of the blind spot area serve to differentiate a spurious optic neuritis from a papillitis or papilledema.

Frequent perimetric studies of the enlarging blind spot, associated with similar studies of the peripheral and intermediate zones of the visual field and the macular area are of definite help in determining the time for operative interference.

The significance at one time ascribed to various types of dyschromatopsias (interlacing color lines and inversion of the color fields) as indications of increased intracranial tension, even in the absence of papilledema, has not been justified by modern methods of field-testing.

Scotomas and hemianopsias in the subjects of true migraine, are due to angiospasm and not to increased intracranial pressure.

Certain contractions or depressions of the visual field, noted in feeble, elderly persons, in patients with cerebral arteriosclerosis, and in the subjects of so-called chronic headaches, are more likely to be due to "impaired cerebration" caused by physical weakness or disease, than to increased intracranial pressure.

Although increased intracranial pressure contributes largely to the production of papilledema interpreted in the field by a pericecal sco-

toma, it is difficult to believe it is an entirely unassociated factor; it may be present even in high degree without causing disc-edema. Moreover, as Adson and W. L. Lillie (17) point out, its general symptoms may be absent in cases of local intracranial lesion, for instance, a leptomeningitis of otitic origin, and yet papilledema may be present.

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CHAPTER XXI

BRAIN CHANGES IN INCREASED INTRACRANIAL PRESSURE¹

GEORGE B. HASSIN, M.D.

INCREASED intracranial pressure occurs whenever the skull cavity harbors more contents than it can keep under normal conditions. It may be produced experimentally or by pathologic conditions, such as abscesses or tumors within the skull cavity. The latter were utilized by me in the present studies. Of 17 tumors studied, 4 were meningeal and pressed on the hemispheres-frontal, occipital, temporal and parietal; 4 were infiltrating tumors (1 of the frontal lobe and 3 of the basal ganglia); 3 were tumors of the pons (1 of these involved the fourth ventricle); 2 were in the ponto-cerebellar angle and 3 were multiple tumors (tuberculomas); 1 was a hypernephroma. In addition, a number of carcinomatous metastatic tumors of the brain, previously studied and reported (1), have been used.

The majority of the tumors affected the brain from the outside, pressing on it, that is to say, they were extracerebral. Occupying space normally assigned to the brain tissues, they caused increased intracranial pressure and created conditions similar to those produced experimentally by injecting fluids between the skull and the dura; by filling up this space with warm wax or with bags filled with mercury, and by similar procedures. The extracerebral tumors, for that reason, were more suitable than the intracerebral infiltrating types, such as gliomas, tuberculomas or metastatic carcinomas. As pointed out elsewhere (1), the changes caused by the latter variety are either mechanical, the result of direct pressure by the tumor mass, or biochemical, which for want of a better term were designated toxic encephalitis. Such tumors were utilized for control or contrast studies, the main attention having been paid to tumors of the former

¹ From the Pathology Laboratories of the Research and Educational Hospitals, University of Illinois, and the Illinois State Psychopathic Institute.

variety in which the outstanding clinical phenomena were those of increased intracranial pressure.

The types of pathologic specimens studied are shown in figures

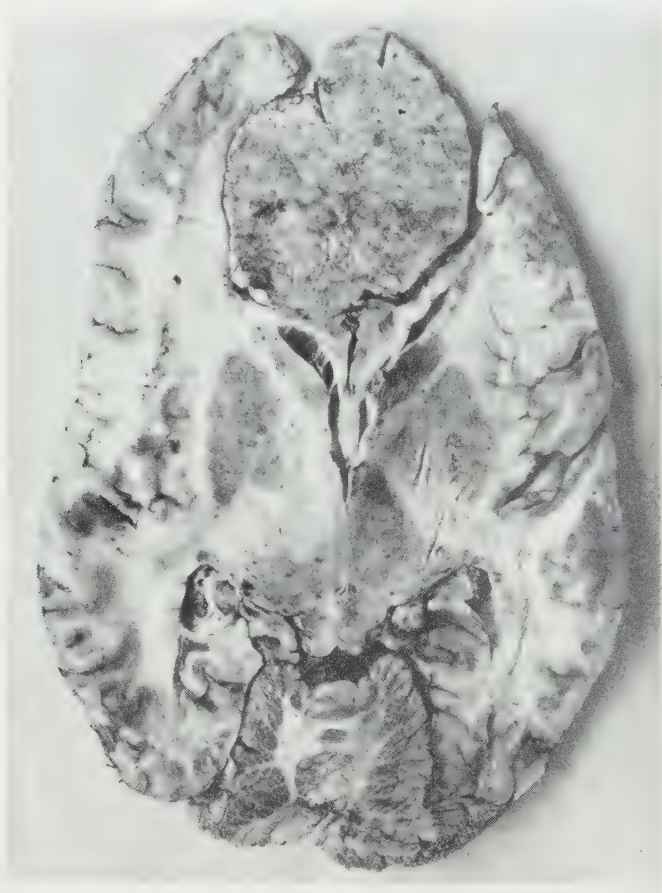


FIG. 100 Invasion of the frontal lobe by a pial endothelioma. This lies in a niche formed by destroyed and atrophied brain tissue.

100 and 101. The former (fig. 100) represents an extreme grade of cerebral compression that resulted in severe pressure symptoms; figure 101 represents a more moderate and probably a more common type. It seemed proper to give a detailed outline of the brain changes

that took place in each type. By contrasting them with the findings in the rest of the cases one may be able to arrive at some conclusions as to the type of histologic changes that are caused by increased intracranial pressure.

In both instances the tumors produced excavations or niches. In case 1 the excavation was of large size and took up almost one-third of the basal portion of the frontal lobe (fig. 100). Its walls encircled the larger part of the tumor, to which they were not adherent; they were irregular in shape and were mainly represented by the white substance of the brain. In other words, the walls of the niche were



FIG. 101. Depression in the left cerebral cortex from pressure by a psammoma

remnants of that part of the brain which bore the brunt of the pressure and which had been replaced by the tumor. This exercised on the brain a direct, purely mechanical, pressure which here therefore was greatest. One may assume that the intracerebral pressure progressively decreased the greater the distance from the tumor. For instance, it must have been milder in the parts of the brain between the walls of the niche and the skull, and still milder in the neighboring portions such as the parietal and temporal lobes. It must have been especially low in remote areas, such as the cerebellum, medulla, occipital lobe, caudal portion of the corpus callosum and the basal ganglia.

The foregoing areas were exposed not to local, but to a remote intracranial pressure. The changes that resulted from both local and remote pressures were studied in celloidin, paraffin and frozen sections, with various staining methods. Of these the methods of Holzer, Bielschowsky and Alzheimer-Mann proved especially valuable. The staining methods of Cajal and Hortega were unsatisfactory, probably because the material was old.

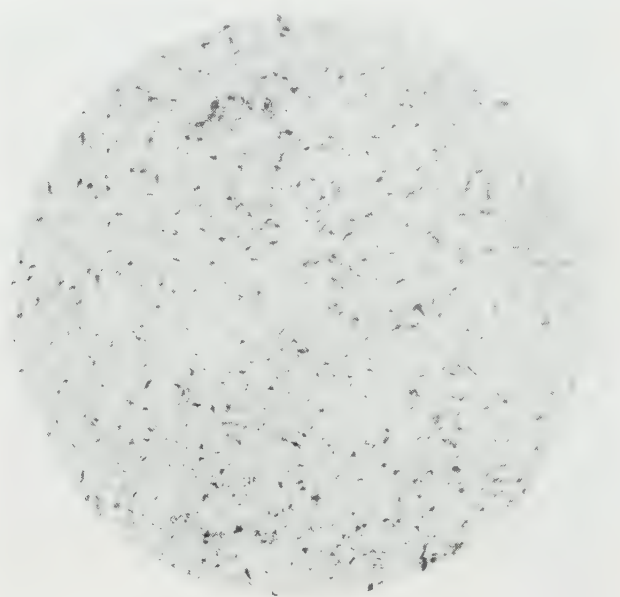


FIG. 102. The walls of the cavity enclosing the tumor in case 1. The numerous dark scattered formations are cytoplasmic glia cells; they are described in the text and reproduced under a higher magnification in figure 103. Holzer stain, $\times 50$.

REPORT OF CASES

Case 1. Pial endothelioma of the base of the frontal lobe

Figure 102 shows the condition of the walls of the cavity or niche that harbored the tumor. The brain tissue here was represented by a multitude of so called cytoplasmic cells—homogeneous cell bodies, irregular in shape, possessing numerous processes and containing an eccentric nucleus rich in chromatin. The cell bodies were always of

large size. Some appeared (fig. 103) as monster cells, with processes of great length and thickness (fig. 104), often arranged in thick bundles. Few cells, of smaller size, were somewhat vacuolated, when they resembled gitter-like structures. Many monster cells contained more than one nucleus which was sometimes unusually large and was often situated at the very edge of the cell body while the processes of the cell bodies were sometimes so abundant and massive that they appeared as a dense network covering the visual field.



FIG. 103. Monster glia—a higher magnification of some glia cells reproduced in figure 102. Holzer stain, $\times 560$.

Aside from the cytoplasmic glia, the walls of the niche contained numerous so called glia nuclei (oligodendroglia cells) scattered over dense bundles of thin glia fibers mixed with blood vessels and capillaries. The oligodendroglia nuclei were quite large and rich in chromatin. Therefore, they appeared unusually bright and showed a distinct membrane. In some nuclei the chromatin granules were rather scarce, but regressive changes, such as swollen oligodendroglia,

were absent. Ganglion cells in these areas were scarce and were present only in some portions of the wall of the niche. They were in a state of necrobiosis and it required, therefore, some effort to identify them. They appeared very pale and vacuolated, and their processes were either swollen and homogeneous or broken up and missing.

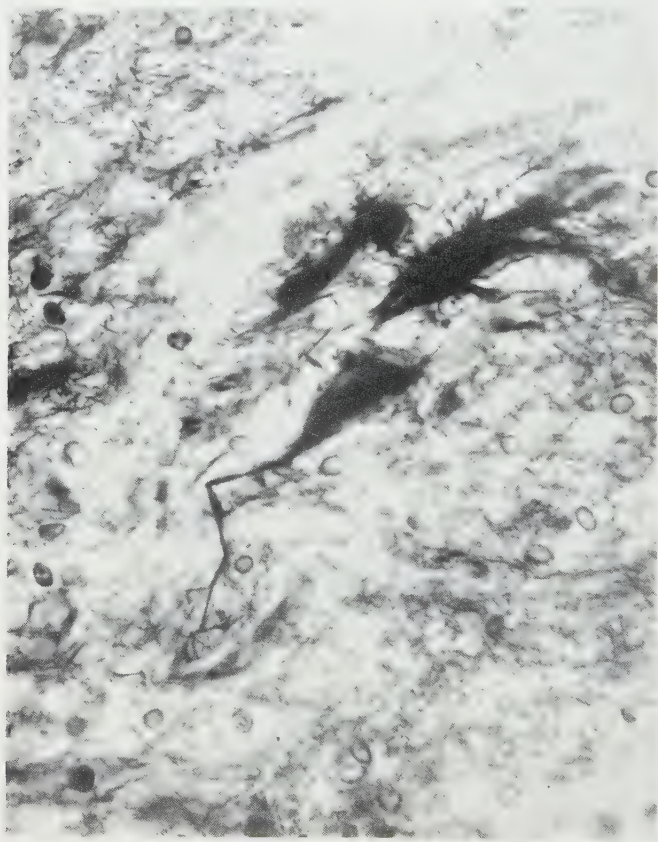


FIG. 104. A monster glia cell with a thick, massive, branching process. Holzer stain, $\times 1100$.

Nerve fibers were absent; the blood vessels were hyperemic and congested, their walls hypertrophied. No occluded blood vessels were present, nor were there signs of inflammation, such as plasma cells, lymphocytes and similar hematogenous elements. There were

no foci of softening such as are seen in encephalomalacia, but many gitter cells filled with lipoids were present within the adventitial spaces of the blood vessels and in large numbers among the fibers or interspaces of the white substance (fig. 105). These were crowded with large globules and drops of lipoids forming masses that much resembled the β -type of Jakob's gitter cells. The lipid masses were so dense that the cell nuclei were overshadowed and could be seen only in exceptional cases. In short, the wall of the niche exhibited

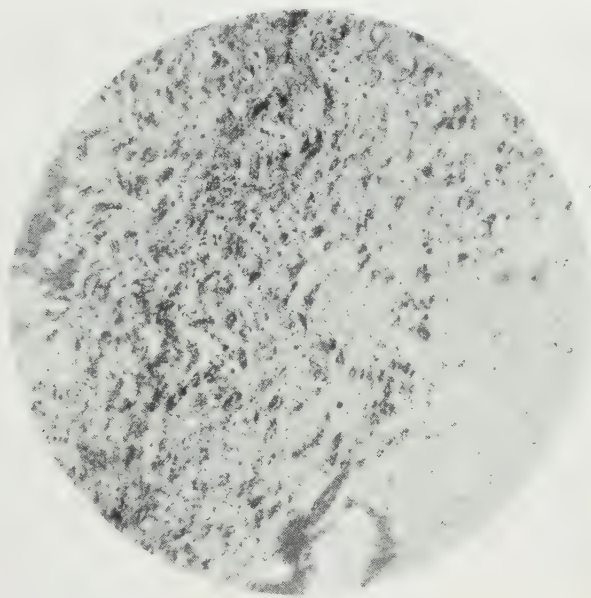


FIG. 105. Masses of lipoids in the interspaces of the white substance in the immediate vicinity of the tumor. Scarlet red and hematoxylin stain, $\times 60$.

far advanced degenerative phenomena and much resembled what is known as a glia scar.

Areas adjacent to the walls of the niche and situated between them and the cortex were fairly well preserved, with both the gray and white substance well represented and defined. The ganglion cells exhibited the usual array of layers, but the subcortex showed a mass of cytoplasmic glia cells, blood vessels and well preserved nerve fibers. In

some places, portions of gray matter were divided from the cortex by thick bands (fig. 106) of glia scar tissue. In general, the changes in the areas adjacent to the tumor were similar to those in the walls of the niche, but were rather less extreme. They also differed in containing so called areas of rarefaction (fig. 107). These were small or large, were often situated around the blood vessels and capillaries and consisted of reticular tissue that was made up of large vacuoles

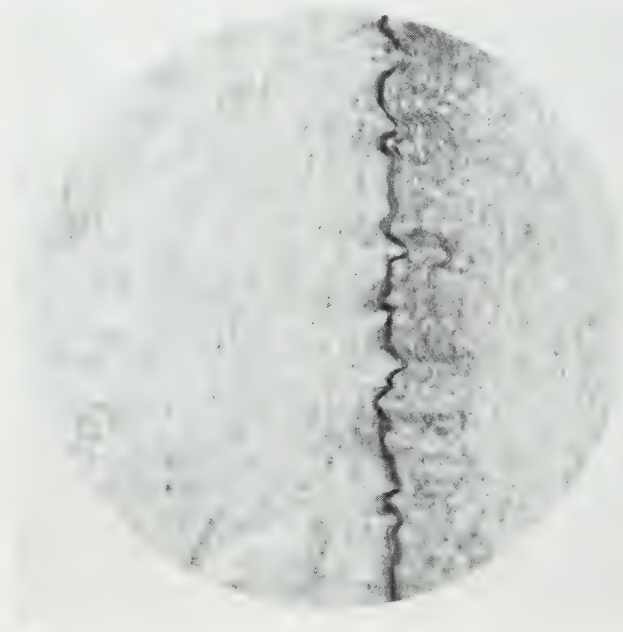


FIG. 106. Bundles of glia fibers forming a broad band in the cortex outside the destroyed area. Holzer stain, $\times 120$.

divided from one another by delicate glia walls. They were usually empty, sometimes they contained an amorphous ill-defined substance.

Of the neighborhood areas, the corpus callosum exhibited a number of degenerative phenomena—from formation of vacuoles to that of a glia scar. The vacuoles were for the most part empty but many contained various types of gitter cells or other gliogenous formations, such as myeloclasts and myelophages. In addition there were numerous cytoplasmic glia cells, oligodendroglia cells and accumulation of

lipoids. The nerve fibers of the corpus callosum exhibited marked phenomena of secondary degeneration, but the majority were merely tumefied; in others, the myelin was broken up into globules and enveloped by glia. Blood vessels and capillaries were very numerous; their intima was hypertrophied and the adventitial spaces were filled with lipoids. The changes described were present only in the cephalic portion of the corpus callosum (its genu) which was adjacent to the



FIG. 107. Areas of rarefaction (cortex). Van Gieson, $\times 70$

tumor. They may, therefore, be looked on as the result not of an increased intracranial pressure, but of the pressure by the tumor itself. In the caudal portion (splenium) the changes in contrast were rather mild. They showed mainly as swollen oligodendroglia, vacuole formation, excessive vascularization and accumulation of lipoid substances. Oligodendroglia cells were very numerous. They were often arranged in long rows parallel to the blood vessels and in many instances they appeared as if in pure culture (fig. 108). The vacuoles

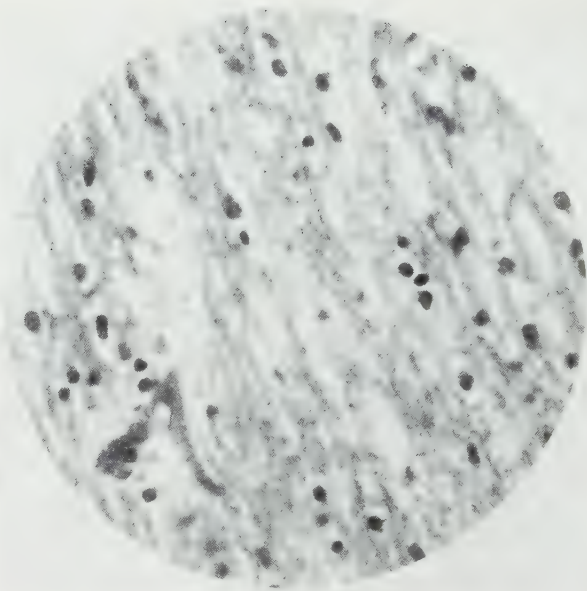


FIG. 108. Oligodendroglia cells within vacuoles, some of which are devoid of contents. Holzer stain, $\times 560$.

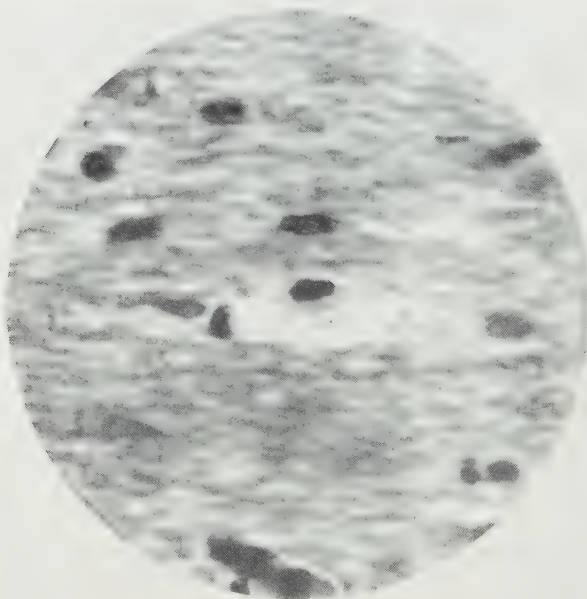


FIG. 109. Granular glia cell within a distended tissue space. Holzer stain, $\times 1000$.

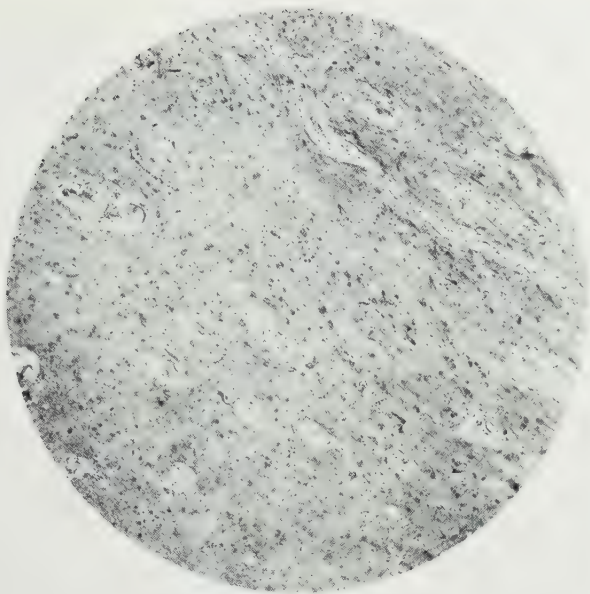


FIG. 110. Optic nerve. Cytoplasmic glia cells and numerous blood vessels; adventitial spaces are filled with lipoids. Scarlet red and hematoxylin stain, $\times 60$.

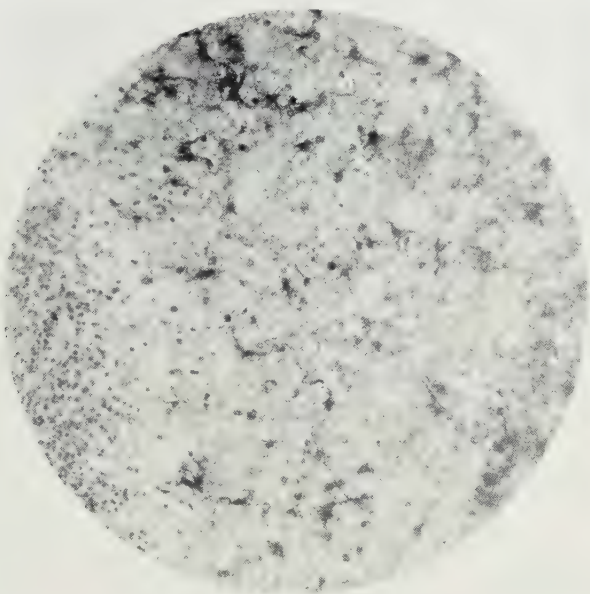


FIG. 111. Cerebellum. Glia proliferation in the white substance. Holzer stain, $\times 170$.

usually contained swollen oligodendroglia cells, many of which dropped out, leaving empty spaces, while many contained a generous amount of cytoplasm which was mostly finely granular (fig. 109). The blood vessels were numerous and as a rule patent; a few capillaries appeared partially occluded with signs of softening in the surrounding parenchyma, but with masses of gutter cells in the adventitial spaces.

A condition similar to that in the corpus callosum was also en-

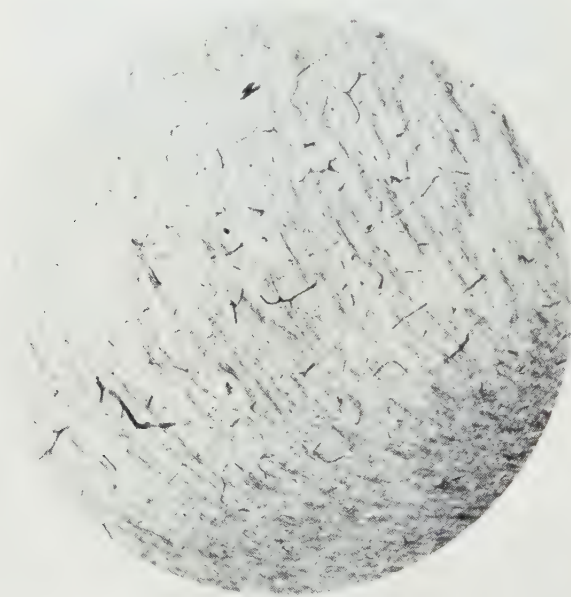


FIG. 112. Occipital lobe—excessive vascularization. Bielschowsky stain combined with the method of Alzheimer-Mann, $\times 70$.

countered in the optic nerves and the chiasm. These structures were missing in this case, but they were carefully studied in other cases of increased intracranial pressure. In such cases the changes were practically the same as in the walls of the niche as figure 110 shows, that is to say it was in a state of advanced nerve degeneration that resulted in a glia scar formation.

In the remote areas (occipital, cerebellum, medulla oblongata) the changes were mostly in the subcortical white matter, in the form of

excessive glia proliferation (fig. 111), while in the gray substance the changes showed as satellitosis and neuronophagia. In the occipital lobe the subcortex was excessively vascularized (fig. 112) and in addition it exhibited numerous areas of rarefaction, mostly around the blood vessels and capillaries. The areas of rarefaction were also in evidence in the basal ganglia which otherwise showed no particular changes. I wish also to call attention to the condition of the cerebellar hemispheres. The left was macroscopically smaller than the right, probably because it was subject to higher pressure. Microscopically it exhibited much more extensive changes than on the right side and these were especially in evidence in the white substance.

The subarachnoid space, as a rule, was greatly distended; the pial blood vessels were very hyperemic and often surrounded by extensive hemorrhages. It was rich in cell elements, such as lymphocytes, mesothelial cells, fibroblasts and gitter cells. The choroid plexus showed swollen tuft cells which were expanded and in many instances resembled gitter cells.

Of the cranial nerves only the fifth, sixth and seventh were studied. They showed no changes.

From the short review of changes in the areas remote from the tumor one may gather that essentially they resembled those present in the areas which were exposed to the direct pressure of the tumor. In other words, the changes that were caused by the increased intracranial pressure were practically of the same kind as those produced by the tumor itself. The differences were quantitative rather than qualitative, but in either condition the changes were degenerative, mechanical in origin, and in proportion to the severity of the pressure. Marked near the tumor, they gradually subsided the farther one passed away from it and in some regions, such as the basal ganglia, were hardly noticeable.

The changes here described, especially near the tumor, in the frontal portion of the corpus callosum, and in the optic nerves are irreparable. They should, however, be expected only in cases in which the intracranial pressure is very high, or in which it is of long duration. When these factors are not marked, the brain changes are much milder and may recede to end in recovery. Such changes were present in the following case.

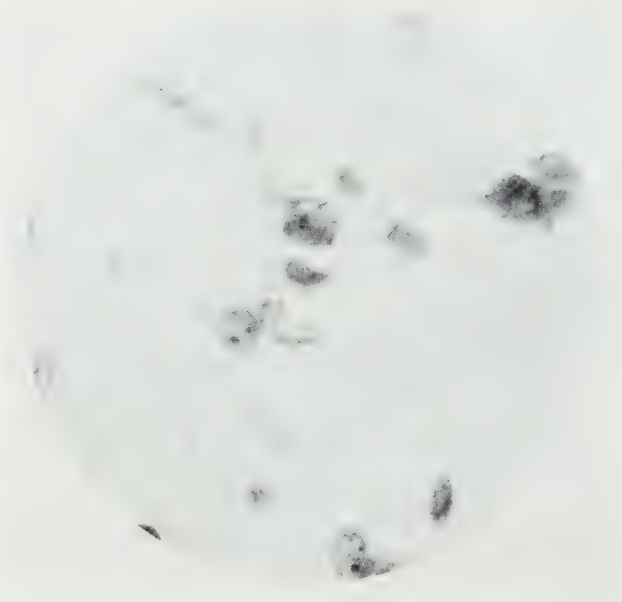


FIG. 113. Blue granules within the ganglion cells as described in the text
Toluidin blue, $\times 1000$.

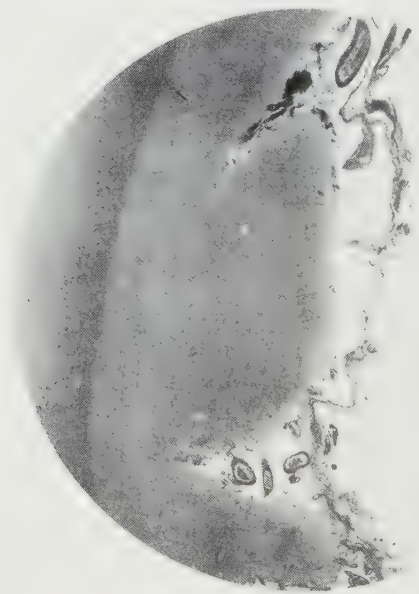


FIG. 114. Pia arachnoid of the compressed area. Case 2. Van Gieson

Case 2. Calcified endothelioma (psammoma) of the dura

In this case a depression (fig. 101) was produced in the left second frontal convolution by a calcified tumor of the dura (1 inch by $1\frac{1}{4}$ inch). The niche produced by the pressing tumor was not as deep as in the previous case and its walls were not destroyed. The brain not only retained its normal shape, but even the sulci and the convolutions were normal. The left lateral ventricle appeared narrower than

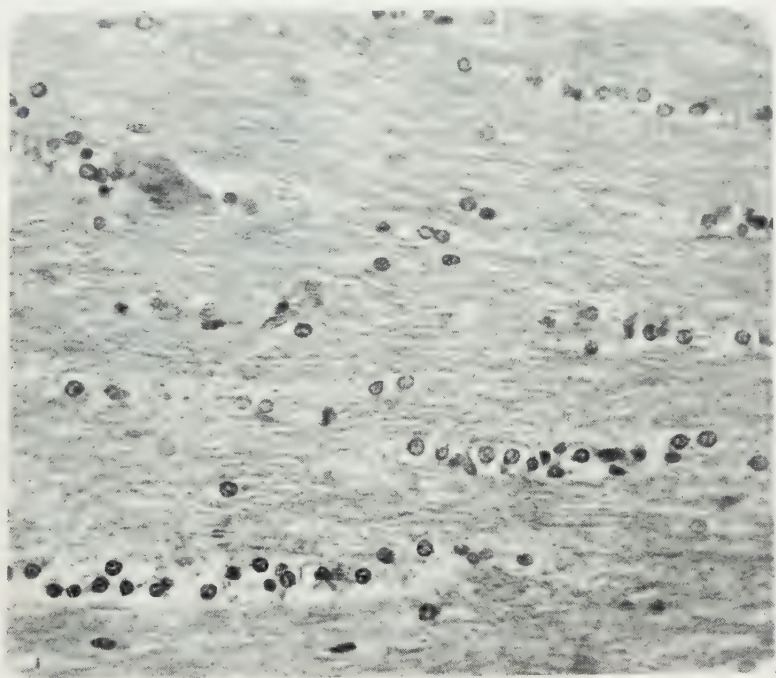


FIG. 115. Swollen oligodendroglia arranged in rows. Holzer stain, $\times 350$

the right which was somewhat distended. The collapsed left ventricle evidently was caused by the pressure and thus made room for the tumor. In case 1, room was made by atrophy of the compressed brain tissues.

Microscopic examination. The depressed cortex exhibited a normal array of layers. The subpial layer or stratum zonale appeared rather wide and contained numerous astrocytes. The ganglion cells exhibited mild degenerative phenomena, such as chromatolysis, homo-

geneous tortuous processes and neuronophagia. The majority contained numerous blue granules which densely covered the cytoplasm, invaded the dendrons and the glia and were also abundant in the walls of the blood vessels and capillaries (fig. 113). These were very numerous and hyperemic with no signs of inflammation or other changes. Sections stained with the method of Holzer² exhibited numerous vacuoles, a great number of spider cells in the subcortex, an enormous increase in glia nuclei (oligodendroglia) and excessive cortical and subcortical vascularization. The pial vessels were also markedly hyperemic, the lumens were patent and the walls hyperplastic. The pia arachnoid was distended (fig. 114) and its meshes enclosed large hemorrhagic foci around distended blood vessels.

Of the large ganglia, the right caudate nucleus (on the side opposite the pressure) contained a fairly large focus of softening and numerous areolar foci. These foci of rarefaction were also in evidence in the left caudate nucleus as well as in the optic thalami and the corpus callosum. The latter also contained many vacuoles, mostly without contents, and masses of glia cells arranged in foci. Many of the glia cells had an expanded cytoplasm, faintly stained and homogeneous, without processes and with a peripheral nucleus rich in chromatin. Such expanded cells mostly adendritic are what the German authors designate as "gemästete" cells. Other cells again showed as swollen oligodendroglia and are pictured in figure 115. The oligodendroglia cells were often so dense that they resembled what Nissl described as "Gliarsen"—several cytoplasmic glia cells are blended and appear as one protoplasmic cell body with several nuclei. They were also numerous in the medulla and were usually loaded with blue pigment granules. In the subependymal regions the foci were prominent and the glia was mostly cytoplasmic. When stained with the method of Holzer it also appeared as such in the optic nerves, which otherwise were practically normal. No particular changes were found in other regions of the brain.

The noteworthy changes in this case were softening of the left caudate nucleus, cytoplasmic glia in the subcortex, manifest glia reaction in the corpus callosum and quite marked areolar foci. Of these changes the softening was the most serious, the rest were less so. It is rather remarkable that the focus of softening was located on the

² Holzer's method is used by me in Warkany's modification.

healthy side of the brain, where the intracerebral pressure must have been lower than on the opposite side—the side of the tumor. In only one other case did I find a focus of softening (in Ammon's horn); that is in 2 of 17 cases studied. It would not, therefore, be proper to consider this pathologic condition the result of increased intracranial pressure, for it was absent in cases in which the latter was very high. The increased pressure was, however, most likely responsible for the

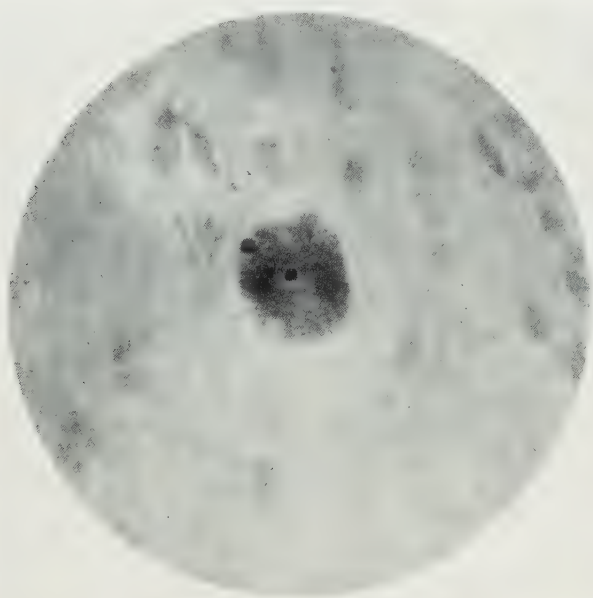


FIG. 116. Basophil-metachromatic substances in the corpus callosum. Alzheim-Mann stain, $\times 1000$.

rest of the changes, such as areolar foci, glial manifestations in the corpus callosum and the subcortex.

Studies of the other cases showed that the pathologic changes may vary in extensity as well as in intensity, that is to say, they may not be so far advanced as in case 1 and may be much more so than in case 2. Much, of course, depends on the localization of the original pressure. For instance, in a case of a tumor of the fourth ventricle with severe pressure on the pons and a resultant enormous dilatation

of the third ventricle and sylvian aqueduct, the ependymal cells were flattened and the subependymal glia appeared fibrous, proliferated and dense. The blood vessels were hyperemic and distended, the walls were hypertrophied and the pons showed numerous areas of rarefaction. The corpus callosum, the optic nerves and subarachnoid space exhibited changes as described in case 1.

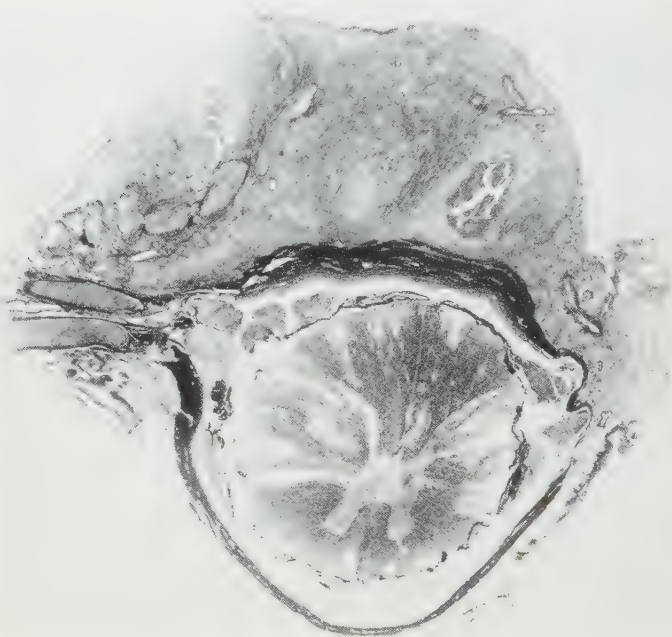


FIG. 117. Spinal cord—pressure changes from an epidural mass containing three abscesses. The cord shows areas of rarefaction, a distended subarachnoid space and glia changes. Toluidin blue.

In the case of a large left temporal lobe tumor (the clinical diagnosis had been that of dementia praecox), in addition to the findings described in case 1, there were present basophil-metachromatic substances in the corpus callosum (fig. 116) with dense foci of oligodendroglia cells and an enormous vascularization of the compressed area. The degenerative changes in the corpus callosum, though present, were mild.

Similar findings, including basophil-metachromatic substances, were also made in a case of left cerebello-pontile angle tumor which formed a large niche and disfigured the cerebellum, the left temporal lobe and the medulla. Blood vessels here were numerous, often new formed, and the glia nuclei (oligodendroglia) showed the same features as described in the corpus callosum.

In a case of infiltrating glioma of the optic thalamus, among other pathologic findings there were numerous small blue droplets and granules as described in case 2. These are catabolic or "Abbau" products, probably what Alzheimer described as methyl blue granules. These of course were not mechanical but biochemical phenomena.

COMMENT

Changes produced by increased intracranial pressure from infiltrating tumors, are somewhat similar to those described with extracerebral tumors, but they are much milder. The quantitative difference may be due to the fact that infiltrating tumors usually do not produce such displacement of the cerebral tissues with such great increase in the intracranial pressure as the extracerebral tumors usually do. Fundamentally, however, the changes as stated, are alike, though they vary in individual cases. These changes are: various stages of degenerative phenomena, with formation of a glia scar; areolar foci or areas of rarefaction, irregularly scattered over the brain including the corpus callosum; excessive vascularization with reactive proliferative phenomena in the vessel walls; degenerative optic nerve changes varying in extensity and intensity; swollen oligodendroglia and distended pia arachnoid space which often contains a variety of cell elements.

It would not be amiss to present here a brief outline of spinal cord changes caused by increased intraspinal pressure. As figure 117 shows the configuration of the spinal cord is preserved, the parenchyma is either broken up or covered by vacuoles and areas of rarefaction or liquefaction, the gray matter is vascularized; the subarachnoid space is patent and the pia, like the glia tissue, is hyperplastic. Other changes here are due to inflammatory conditions (perineuritis) of the meninges.

The similarity between the changes caused by intracranial and intraspinal pressure is thus great; in fact the changes in both pathologic conditions are alike. The only difference is that the zones of

rarefaction caused by increased pressure in the cord are more circumscribed than those in the brain where they are widely scattered. It is commonly agreed that the zones of rarefaction in the spinal cord are, as shown elsewhere (3), the result of stasis of the tissue fluids, from defective drainage. It is highly probable that in the brain the rarefied areas—the vacuoles and zones of rarefaction—are of analogous significance, that is to say, they are the result of defective drainage of some portions of the cerebral parenchyma. Large areas of the latter, however, not exposed to direct pressure, may be drained normally, or with little interference by the tumor, or they may even be drained excessively. Such conditions may account for the fact that in the presence of even large tumors the clinical symptoms of increased intracranial pressure may be mild or absent altogether. On the other hand, local pressure on certain portions of the brain may affect the circulation of cerebral tissue fluids in areas remote from the tumor, cause their stagnation and thus be responsible for remote foci of rarefaction.

In general, the changes due to increased intracranial pressure may be classified as degenerative, associated with diffuse secondary proliferative glia phenomena. They are very similar to the local nerve tissue destruction caused by prolonged mechanical pressure by a large tumor. In other words, their genesis is primarily mechanical. In favor of the mechanical origin of the degenerations speak also the changes in the corpus callosum, where the fibers appear to be damaged by the dilated lateral ventricles, torn by them—a condition not unlike the one produced in Anton's operation (sectioning of the corpus callosum). The more distended the ventricles the more numerous were the fibers that were degenerated and vice versa. The fact that in some cases the genu of the corpus callosum was more damaged than the splenium may be explained on the assumption that here too the mechanical factors were more at play, for the lateral ventricles were more affected (dilated) in the cephalic than in the caudal portion.

When of long standing and of an unusual severity, mechanical influences may lead to actual destruction and atrophy of the nerve tissues and their replacement by a glia tissue scar, as in case 1. In milder instances, as in case 2, no destruction obtains, but mild "irritations" occur which might be termed contusion. Changes in the latter, discussed elsewhere (4), may also be classified as degenerative. In increased intracranial pressure they are combined with changes in

the tissue spaces, lateral ventricles and blood vessels. Such conditions may lead to what Adamkiewicz (5) called condensation, so well seen in figure 101. Here the bulk of the brain tissues become smaller in order to make room for the tumor mass.

The remarkable fact of the subarachnoid space remaining patent and even dilated can be explained by the reactive phenomena in the pia arachnoid. Stimulated by the slow growth of the tumor, the connective tissue and other constituents of the subarachnoid space proliferate. The same may be said of the blood vessels which were always patent and hyperemic; often they were excessive in number, their walls were hypertrophied and hyperplastic. In no instance did they show phenomena that would justify the claim that the histologic changes noted were merely the result of vascular changes.

CONCLUSIONS

Increased intracranial pressure produces quite typical histologic changes in the brain.

They are degenerative, associated with reactive glia phenomena and are analogous to the changes that result from prolonged pressure (by a tumor) on the brain or spinal cord.

The changes are diffuse and noticeable in the corpus callosum, optic nerve, chiasm and optic tract, while in the ganglion cells they are mild.

The degenerative changes are combined with areas of rarefaction which are due to stasis of tissue fluids and accumulation in some instances of catabolic products, such as basophil-metachromatic substances, lipoids and methyl blue granules.

The extent of the changes varies according to the intensity and the duration of the increased pressure.

Generally the histologic changes in pressure are of mechanical origin due, as in corpus callosum, to the actual tearing of nerve fibers or to nutritional disturbances brought on in some parts of the brain by stasis of the tissue fluids.

The subarachnoid space and the blood vessels usually exhibit proliferative reactive phenomena.

In tumors of the brain, the changes produced by increased intracranial pressure are more marked in extracerebral than in the intracerebral types of tumor.

DISCUSSION

The following questions submitted to Dr. Hassin before the Commission, together with the answers to them, are here reported verbatim.

DR. FREEMAN: Does Dr. Hassin believe that these cells have undergone hydropic degeneration?

DR. HASSIN: No. The spaces are merely dilated tissue spaces that resulted from stasis of tissue fluids. This causes breaking down and degeneration of the myelin, a repressive condition which accompanies these phenomena, but here it was not the same thing as hydropic degeneration.

DR. SACHS: In the case, in which the changes in the cerebellum were almost as marked as they were in the parts of the brain nearer to the tumor, is it not possible that there may be some other factor besides that of mere pressure and direct invasion?

DR. HASSIN: In this particular case the pressure lasted for a long time. I did not see the patient myself because the brain had been sent to me from the Canal Zone, with a history of a mental disorder. It did not even contain any reference as to the condition of the fundi. The duration evidently was about eight months. When the pressure is so severe, with such a big tumor, and of so long a duration, the changes, of course, must be widespread and very marked, as it was in this particular case. There were no other causes for the changes in the cerebellum except for the tumor and the duration of the pressure. I couldn't find evidences of such causes, as infection, intoxication or similar conditions.

DR. TAYLOR: Were there any marked changes in the blood vessels?

DR. HASSIN: Yes. The blood vessels showed hyperplastic phenomena in the adventitia and hyperemia. I paid particular attention to the condition of the blood vessels, because of the great importance they are supposed to possess in increased intracranial pressure.

DR. FREEMAN: In view of the papers we heard yesterday concerning the condition of the arterioles in increased intracranial pressure, said to be dilatation with arrested flow, would not Dr. Hassin consider that the anatomic changes which he interprets as active hyperemia might rather be passive hyperemia due to stasis or anoxemia?

DR. HASSIN: Yesterday, we heard of conditions which were experimental, while the conditions presented by me are all pathological from material obtained from human beings. The arterioles in my cases had plenty of time to adjust themselves to the abnormal conditions, and I do not see here any other factors such as you mentioned.

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CHAPTER XXII

NOTES ON CEREBRAL PRESSURE ATROPHY¹

WILDER PENFIELD, M.D.

CONDITIONS well suited for the study of simple pressure in the brain are obstructive internal hydrocephalus, and external hydrocephalus, for under such circumstances the brain is affected only by the pressure and not necessarily by additional toxic factors. Cases have been chosen for study in which there was no active infectious process and no source of toxic absorption.

The pattern of ventricular enlargement which follows complete obstruction, for instance, to the aqueduct of Sylvius, is so familiar as to require little description here (1). There results a symmetrical dilatation of the lateral and third ventricles. The convex walls of the hemispheres become thinner and the optic thalami and striate bodies stand out boldly in the lateral ventricles.

In infants whose cranial sutures are flexible there occurs a disproportionate atrophy of the ventricular walls while the basal ganglionic mass is thinned to a lesser extent. In the adult, whose cranial cavity does not yield, death results at an earlier period from herniation of the cerebellum and medulla oblongata into the foramen magnum, or of the midbrain into the incisura of the tentorium. Thus the duration of the compression is apt to be shorter. But a yielding cranial wall not only postpones herniation of the vital centers downward, it also produces a marked thinning of the cerebrum flattened against that yielding barrier.

Thus when the sutures and fontanelle gape widely the underlying hemispheric wall is found to be markedly thinned. Where the sella turcica is flattened out into the sphenoid sinus, the walls of the third ventricle will be found to be paper thin. If the posterior sutures are more widely separated than the anterior ones it will be found that there is greater cerebral thinning posteriorly.

¹ From the Laboratory of Neurocytology, Presbyterian Hospital, and the Department of Surgery, Columbia University, New York.

For example, in case J. B. (congenital internal obstructive hydrocephalus with a block at the aqueduct of Sylvius, age three months) the cerebral convexities are greatly thinned while the thalamus and corpus striatum have undergone less atrophy (fig. 118). Before the death of this child it had been quite evident that the occipito-parietal

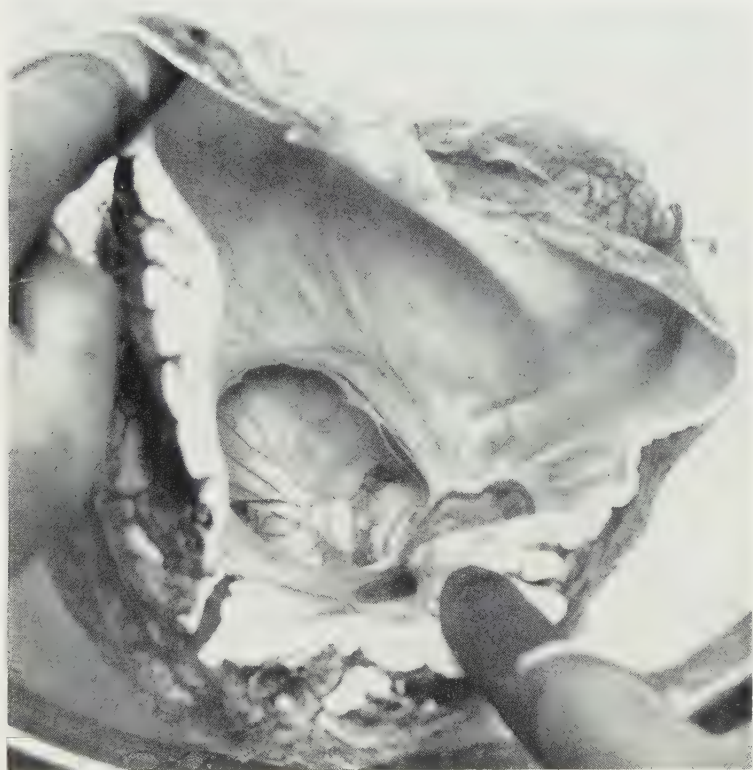


FIG. 118. Case C. B., congenital hydrocephalus, with block in the aqueduct of Sylvius. Age 3 months at death. The left hemisphere has been incised to expose the ventricles.

sutures were more widely separated (about 1 cm.) than the other sutures. Correspondingly the posterior portions of both hemispheres were much thinner than farther forward. Thus the thickness of the translucent post-central cortex was 0.5 mm., and the occipital lobe 1 mm. while the frontal lobe was 15 mm. in thickness (fig. 119). The

amount of this thinning is far out of proportion to any thinning that might have occurred as the result of simple stretching without atrophy.

The ventricular pressure was 320 mm. of water. This pressure must have been exerted equally against all the walls that bounded the ventricles. The yielding of the parieto-occipital sutures seemed

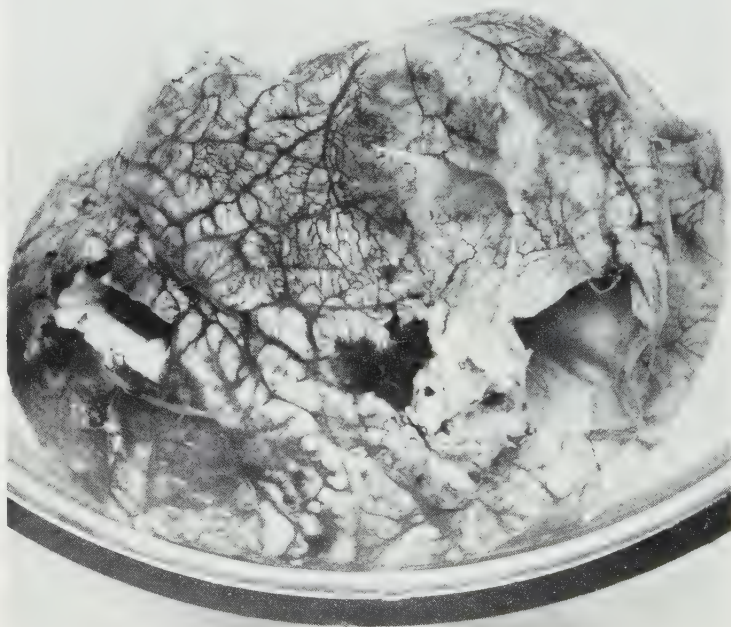


FIG. 119. Same case as figure 118. Note thick frontal lobe as compared with paper thin parietal lobe.

further to handicap the posterior portions of the hemispheres so that atrophy is much further advanced in these portions. It seems likely that such stretching further embarrasses an already compromised vascularization and the decrease in the number of pial vessels in this contrasts strikingly with the marked hyperplasia of these vessels elsewhere in the pia.

Such disproportionate cerebral atrophy is likewise seen in adults with ventricular distension where decompressive operations have been performed. This is illustrated by the case of a boy of eight years (G. B.) who had a spongioblastoma multiforme of the pons which grew forward into the interpeduncular cistern producing a basilar

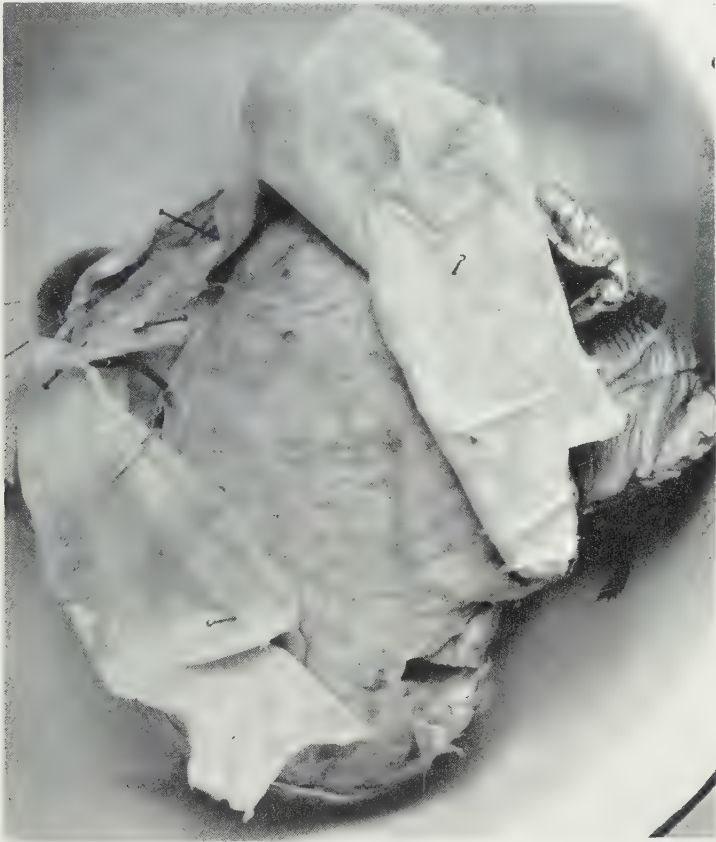


FIG. 120. Case J. M., subdural cyst which contained clear yellow fluid, present over both hemispheres at first, later only over one, age $7\frac{1}{2}$ months.

obstruction. Under suspicion of a cerebellar tumor I performed a suboccipital decompression and found the dura under increased pressure but the cerebellum quite normal in appearance and consistency. The dura was left open and the closure of the muscle was carried out without cerebellar injury.

In a few months the child died and the cerebellum was found to have become remarkably thinned out. Thus the fourth ventricle was enormously dilated and the cerebellar hemispheres reduced to a shell while the other ventricles were only moderately dilated. This cerebellar destruction had all taken place in the few months which followed decompression.

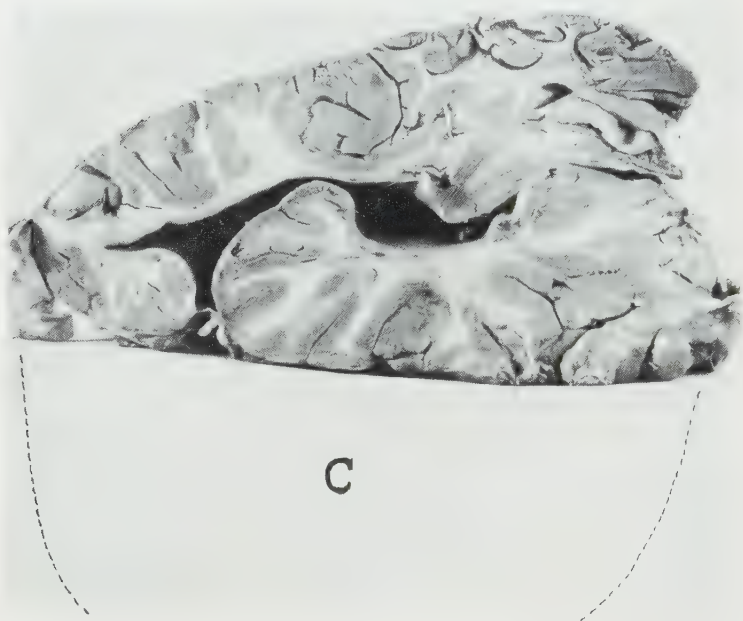


FIG. 121. Same case as figure 120. The dotted line indicates the extent and size of the cyst (C). One hemisphere is pushed into the ventricle of the opposite side.

In a second case (F. V., a woman of thirty-three years, with a perineurial fibroblastoma of the acoustic nerve) I extirpated all of the tumor presented in the posterior fossa but was forced to leave behind tumor tissue farther forward beneath the midbrain. Following operation there was much pressure on the decompression and rapidly increasing cerebellar signs. A second operation was performed six weeks later and we found the fourth ventricle distended to so great a degree that the cerebellar hemispheres between ventricle and muscle were reduced in thickness to a few millimeters.

In retrospect it would have been better to have split the tentorium in the hope of temporarily relieving the block at the base. This might



FIG. 122. Case M. G., congenital hydrocephalus, block in the aqueduct of Sylvius, and absence of the corpus callosum, age 10 months.

well have preserved the cerebellum for some time. However, we must be concerned here only with the pathological aspects of this case and ignore for the present the human and surgical aspects.

In both of these cases substitution of a wall of muscle for bone and dura resulted in dilatation of the fourth ventricle and rapidly progressive cerebellar destruction, whereas before the decompression the cerebellum in its unyielding compartment had suffered little from the



FIG. 123. Case C. N. F. Internal hydrocephalus secondary to leptomeningitis with block at the pontine cistern.

spinal fluid pressure. The pressure in the other ventricles which did not become so extremely distended must have been the same as that in the fourth ventricle of these cases.

Thinning of the cerebral vault with comparative preservation of the basal ganglia is seen only when the vault is forced against a yielding

cranium from within. On the contrary this disparity does not obtain when the fluid pressure is applied to the brain from without. For example, in the case of J. M. (external hydrocephalus in a child seven and one-half months of age, whose head enlarged rapidly after



FIG. 124. Case C. B., congenital hydrocephalus with block in the aqueduct of Sylvius, age 3 months.

birth) there was a large cyst (fig. 120) filled with clear yellow fluid which occupied the whole left half of the cranial cavity and extended over to the right, flattening the brain out against the right side of the skull (fig. 121). The pressure in this cyst varied from 240 to 330 mm.

of water and yet there is not, to gross examination, any more atrophy of the cerebral convexity than there is of the basal gangliar masses.

A further case in point may be cited (M. G., infant of two months whose head had enlarged progressively from birth. In this case there

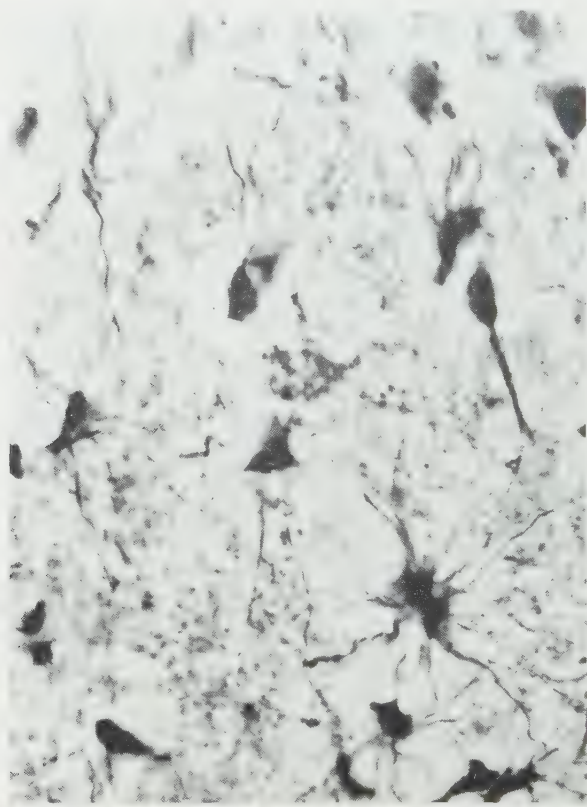


FIG. 125. Astrocytes with the long slender expansions produced by pressure. This was taken from the very thin cerebral cortex shown in figure 119. Cajal's gold chloride stain.

was a deficient corpus callosum and the fluid pressure of 450 mm. of water was exerted against the brain which was flattened against the base without any stretching force (fig. 122). Here again, there is little disproportion between the size of the cerebral cortex and of the basal gangliar mass.

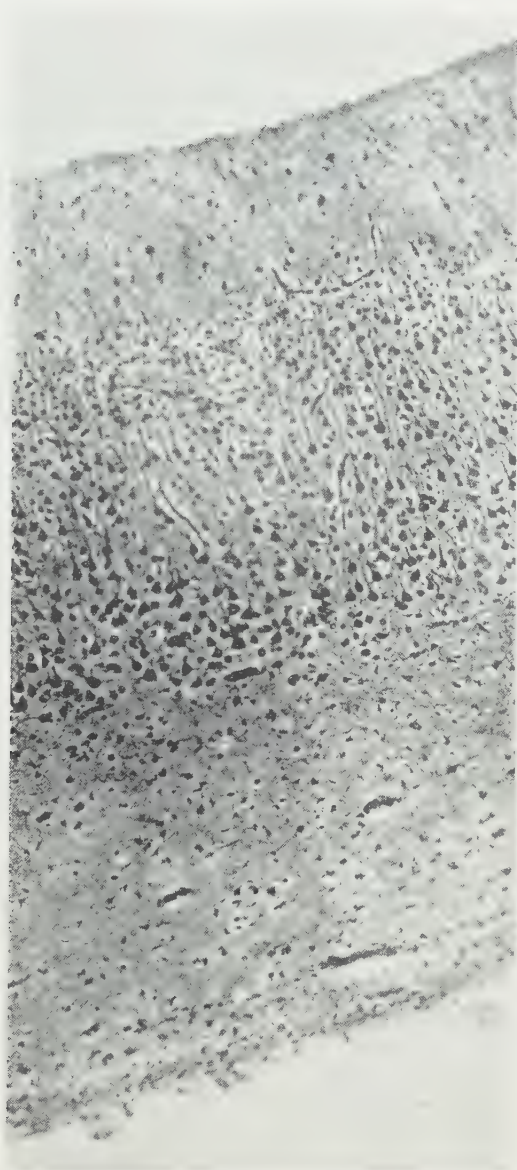


FIG. 126. The full thickness of brain at its thinnest point as shown in figure 119. Note grey and white layers.

One further observation may be made from the consideration of gross specimens of cerebral pressure atrophy. Ventricular distention

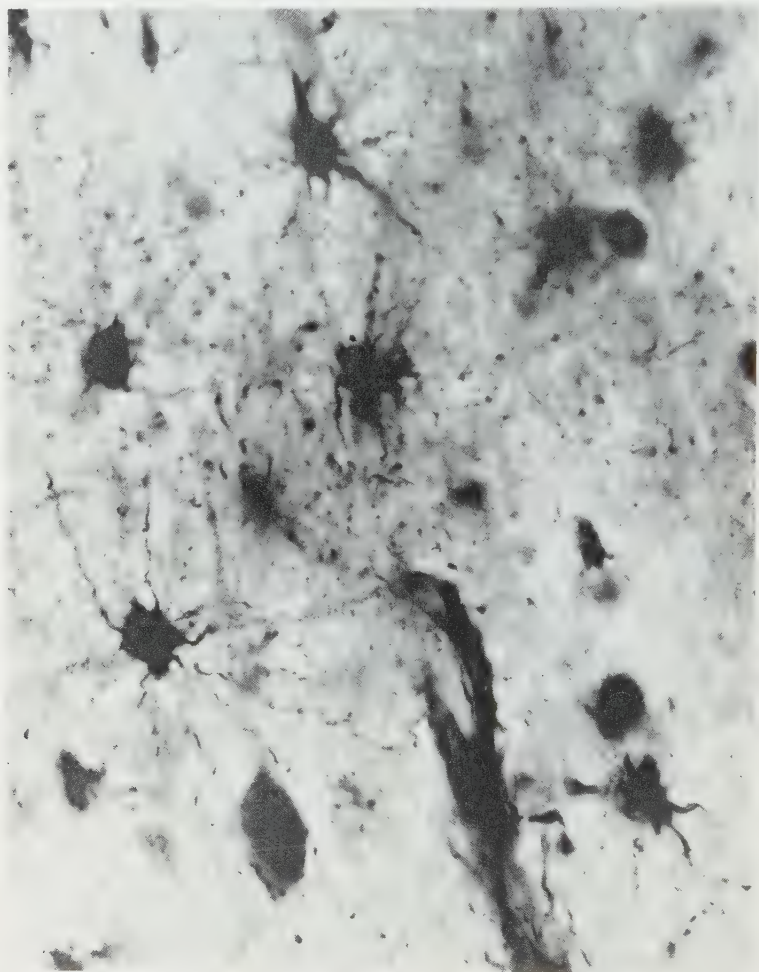


FIG. 127. Astrocytes with long slender, tortuous expansions from the white matter of the thicker frontal lobe shown in figure 119.

results in a much greater destruction of white matter than of grey (fig. 123). If the various layers yielded to pressure equally, a smooth ventricular wall would be found even in advanced atrophy. But this

is not the case as shown in figures 123 and 124. The cortical grey matter is more resistant to ventricular distention than the white

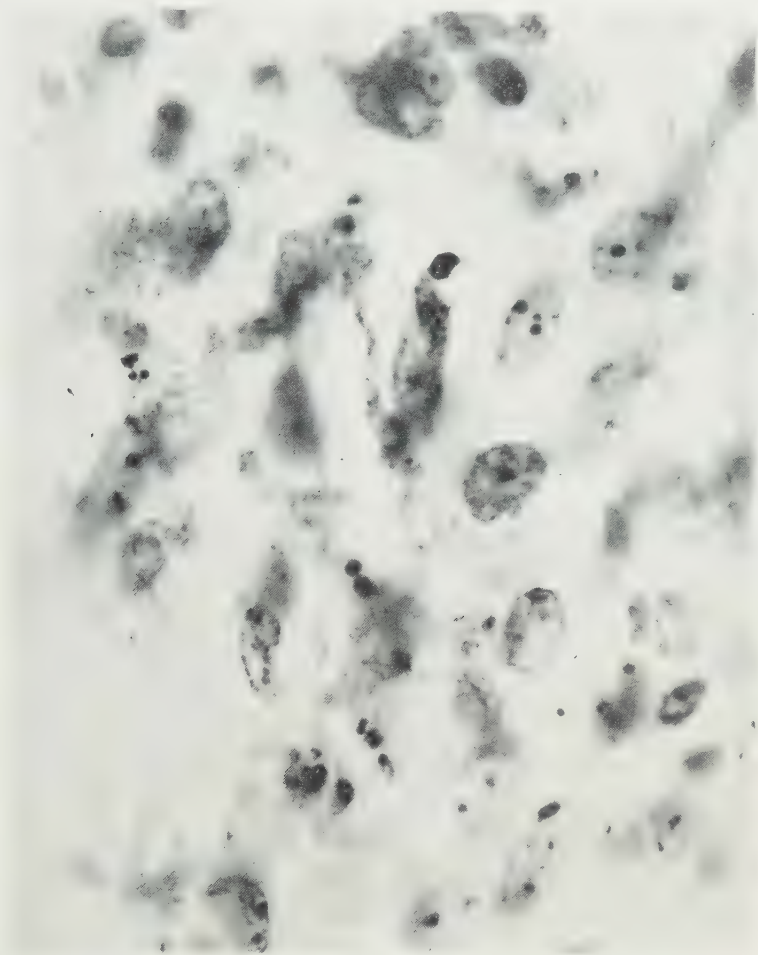


FIG. 128. Phagocytic compound granular corpuscles beneath the ependyma of the thin brain shown in figure 126. Silver carbonate stain.

substance with the result that the fissures form projections into the ventricle. If the flattening process be carried far enough these inverted gyri again become ironed out as in the thin portions of the

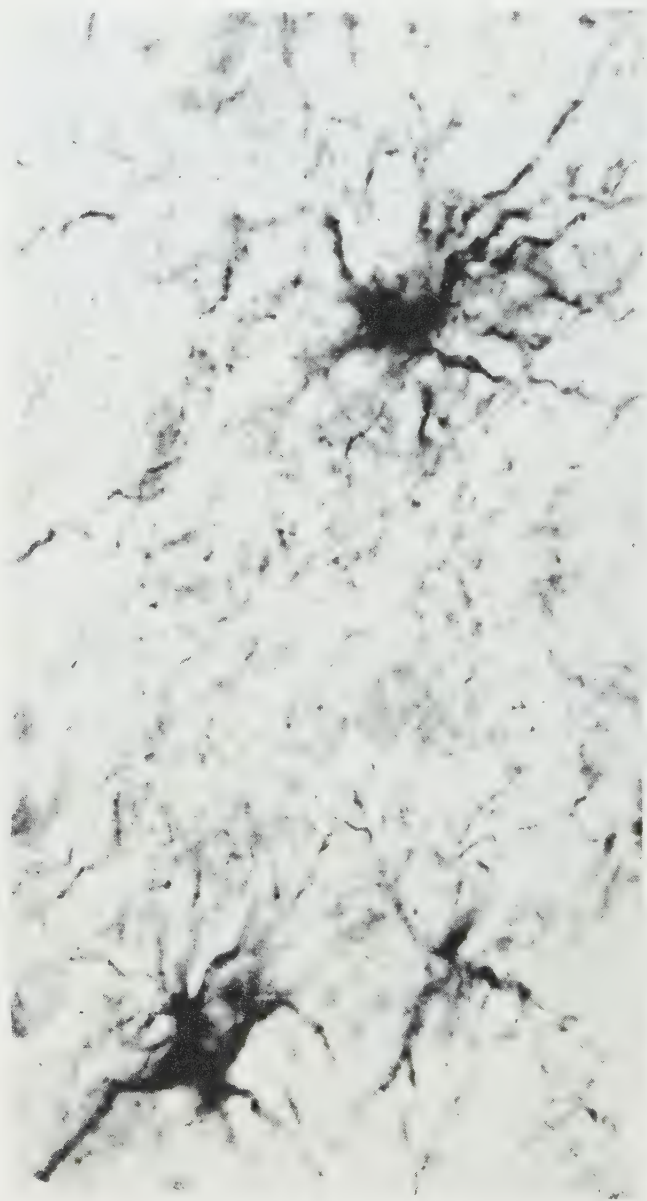


FIG. 129. Astrocytes with somewhat elongated and tortuous expansions from the cerebral hemisphere compressed by the cyst illustrated in figures 120 and 121. Cajal's gold chloride stain.

brain shown in figure 118. Microscopically, moreover, more fat laden phagocytes are found in the white matter and the neuroglia changes are more marked than in the grey matter as will be shown below.

MICROSCOPIC CHANGES

It is a well-known fact that in the atrophy of cerebral tissue which accompanies simple ventricular distention, the arrangement of neu-

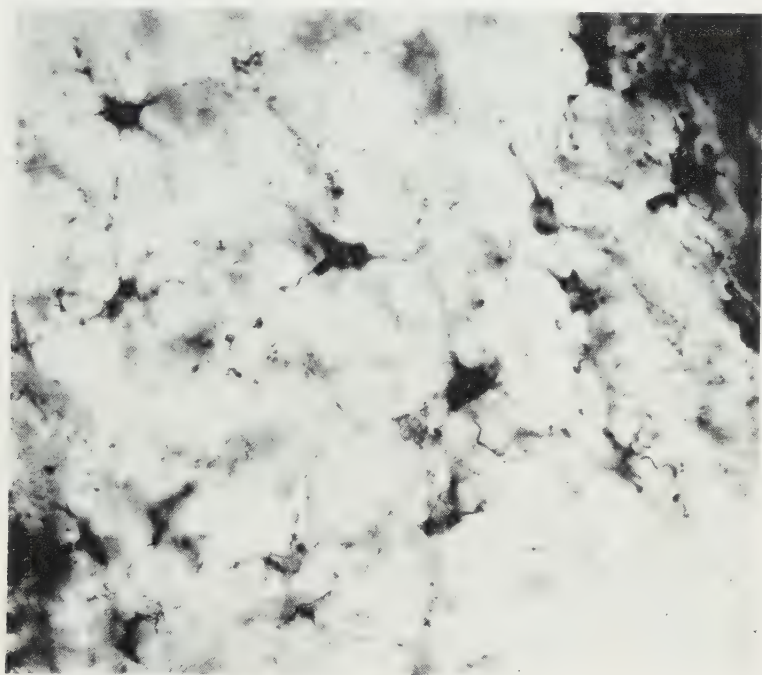


FIG. 130. Astrocytes from the cerebellum of the same case as figure 129. The slender, elongated, tortuous expansions are probably due to the high pressure.

rones is strangely little altered. The various convolutions and their nervous structure can be readily homologized with that of the normal brain (Orton (2)). The nerve cells contain Nissl substance and may show little alteration from normal except for flattening and some pyknosis even in the presence of very marked cerebral thinning.

In other types of cerebral atrophy such as that associated with lesions of arteries or diffuse processes, such as that which is seen in general paresis, there is a marked gliosis. This over-growth of astrocytes is so frequently encountered that Nissl at one time made the assertion that it was the invariable accompaniment of lesions of the brain.

On the contrary, however, in simple pressure atrophy of the brain, there is no such gliosis. To return to the case C. B., illustrated in figures 118 and 119 one finds that the astrocytes of the frontal lobes are if anything more scattered than in a similar field of a normal brain showing that destruction of these cells must have accompanied the atrophy. The cells themselves possess very numerous expansions which radiate outward long distances like the branches of a willow (fig. 125). These expansions are not thickened but are quite slender and often curved as though they had grown in length after the extremity had reached its destination. In the white matter of the thinner cerebral cortex (fig. 126) which, as described above is less than 1 mm. in thickness, the astrocytes show similar characteristics and the long expansions are still more curly (fig. 127). The expansions of such astrocytes come to resemble the roots of a plant in dry, barren soil which sends many slender feelers great distances in search of nourishment.

The astrocytes of the grey matter on the other hand are much more nearly normal. More fat can be stained in the white than in the grey matter and more compound granular corpuscles. These phagocytic cells are seen to be most numerous just beneath the ependyma (figure 128). Thus the microscopic picture bears out the gross evidence that in ventricular distension atrophy of white matter is much greater than of grey.

When it is borne in mind that the wall of the hemisphere in the last mentioned case (C. B.) represents what was once a very much thicker structure it is obvious that many astrocytes must have disappeared while the remaining cells have undergone a process of attenuation and elongation. In the case of external pressure (case J. M., illustrated in fig. 121) the astrocytes of the cerebral white matter have numerous willowy expansions (fig. 129) and those in the granular layer of the cerebellum possess slender unusually irregular expansions (fig. 117).

CONCLUSION

Finally, with no pretense of making a complete description, certain aspects of the reaction of the brain to high pressure have been pointed out particularly where the pressure is exerted from within. There is an alteration in the form of neuroglia astrocytes which is associated with long continued pressure and probably with pressure atrophy of the cerebral tissue. Such cells are found in areas of brain where compound granular corpuscles, containing fat, also bear testimony to cerebral atrophy. The astrocyte expansions are long, willowy and numerous but slender. The expansions are sometimes quite curly and the cell body may be flattened and pyknotic.

In ventricular distension from whatever cause the cerebral atrophy is more marked in the white matter than it is in the grey. It is suggested that this may be in part due to the lesser vascularity of white matter and to the fact that pressure is exerted directly upon it.

A most important *principle* involved in the destruction of brain tissue by ventricular pressure is the fact that those portions of cerebrum or cerebellum undergo the most rapid destruction which are pressed against a yielding surface.

Consequently, in an infant, hydrocephalus produces most marked atrophy in the convexity of the cerebrum which is pressed against the yielding cranial vault; the third ventricle becomes paper thin when the sella is much depressed; decompressive operations result in progressive destruction of the underlying brain if there be distention of the ventricle in that region. For example, suboccipital decompression results in rapid destruction of the cerebellum if the block to the outflow of cerebro-spinal fluid lies in the basal cisterns *peripheral to the fourth ventricle*. This is evidently not the case where the decompression is placed over a brain which is enlarged locally by a neoplasm or by some other expanding process.

It would seem that possibly the stretching which is permitted by a yielding wall embarrasses circulation within the pial vessels while an unyielding wall allows the circulation greater freedom because the pia is not stretched, although the pressure exerted through the distended ventricular system must be the same in all directions.

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CHAPTER XXIII

X-RAY EVIDENCES OF INTRACRANIAL PRESSURE

HARRY M. IMBODEN AND CHARLES WADSWORTH SCHWARTZ

THE recognition of changes in the skull due to pressure is simply the recognition of bone atrophy, but it must be clearly borne in mind that atrophy may also occur without pressure, such as, for instance, the so-called senile bone atrophy. It is, however, usually possible to differentiate between atrophy produced by these two causes. The senile atrophy never produces distortion. It is generalized and can be demonstrated elsewhere in the body. Also the age of the patient and history of the case will usually allow differentiation. Pressure atrophy, on the other hand, shows itself in two ways, either generalized or localized. In the generalized type we have as a rule convolutional atrophy which, of course, is nothing more than increased depth of the convolutional digitations, occasionally as in the young, separation of the sutures, and nearly always atrophy of the bones of the base. The changes produced by generalized increased pressure, are usually permanent changes so that in after life, an examination of the skull will reveal the fact that pressure was a factor at one time in the past.

It is often possible to determine with a high degree of accuracy whether the changes seen are due to pressure which is now a factor or pressure which has long since ceased to be. The scars of old pressure usually show themselves as increased visibility of the convolutional digitations which are, however, clearly defined. The bone has ceased to become atrophic, the margins of the depressions are clearly marked. The whole appearance of the inner table is clear cut and distinct. The bones of the base are also clearly defined, and even though it might seem that such structures as the dorsum sellae were somewhat distorted, their outlines are distinct and stand out clearly. On the other hand, if pressure is actually present the inner table will not be clearly defined. This, as one can readily see, would be because of the bone atrophy with the gradual absorption of calcium salts. The convolutional digitations though clearly visible would be lacking in clear

outlines; their margins merge with the surrounding bone. The base would show a lack of detail with or without distortion. The smaller structures on the base, such as the clinoid processes of the sella turcica would be among the first to show a haziness of detail and sharpening

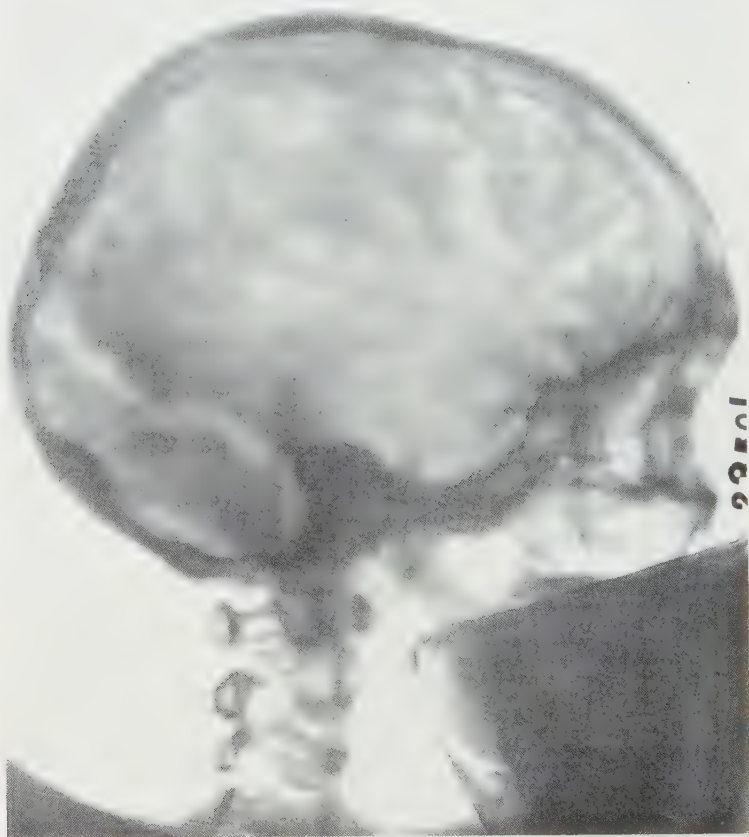


FIG. 131. Active pressure; note lack of clarity in the convolutional markings

which would be more apparent than real, at least in the early stages for the reason that the outside of the bone would lose its visibility before the center.

After one has come to the conclusion that pressure either is or has

been a factor, it is then of interest to see how far we can go in an analysis of the contributing causes. We have, as all know, frequently to deal with abnormally early synostoses of the sutures. When this occurs, growth ceases in that particular part of the skull although, of course, the growth of the brain does not cease. This gives rise to the condition commonly known as craniostenosis. As a result some

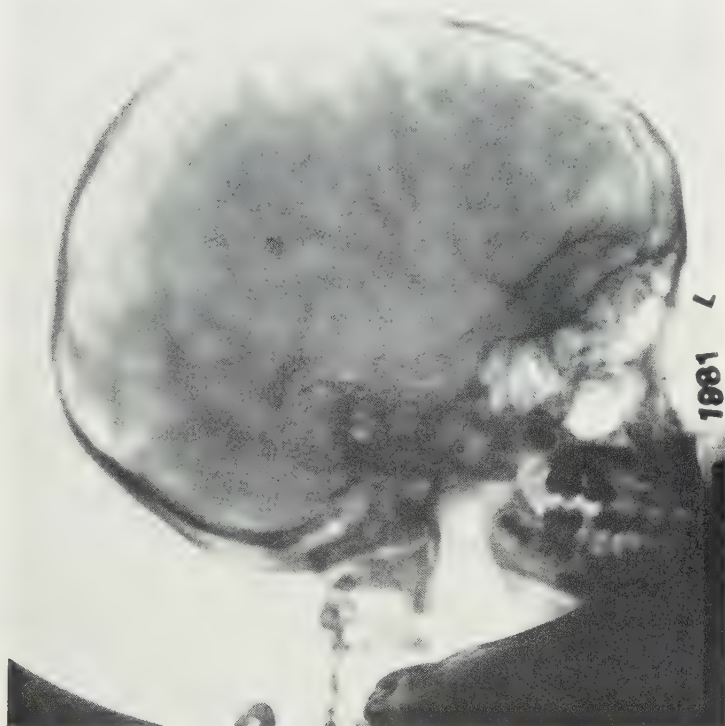


FIG. 132. Scars of old pressure—note clear outlines

compensatory skull development usually occurs and we have numerous interestingly shaped skulls, the classification of which would take too long to go into here. Some of the well known types such as turri-cephaly, scaphocephaly, bathrocephaly, etc., are well known. Nearly always when we run across such a skull in later life we will see the scars of pressure which gave rise to such a formation. We can often

tell, particularly if the patient is seen before middle life, what suture was at fault.

Before continuing further we would like to mention a distribution of convolational atrophy which is often seen in the young and sometimes can be noted in the adult. We have frequently seen the digitations



FIG. 133. Scaphocephaly with old pressure scars

confined to the upper or superior half of the calvarium. Again it will be seen more prominently in the inferior half, principally in the occipital and lower temporal regions. It seems highly probable that the position of the child in utero has a great deal to do with this. If the position is such that the weight presses downward it would pro-

duce more pressure in the superior part of the skull than elsewhere and if the skull be a little more pliable than is usual, due to some nutritional abnormality, the convolutions may well produce their impressions on the inner table. But, after birth, when the position of



FIG. 134. Turricephaly with pressure scars. Probably the result of early union of coronal suture

the child becomes upright and if then the nutritional disturbance becomes a factor, the inferior portion of the skull would be expected to show the greater number of convolutional markings.

The changes commonly seen in hydrocephalics is almost too well

known to mention. We have noted that in the congenital hydrocephalics the head shows the greatest dimensions. Hydrocephalus developing later from some type of intracranial disease usually has the greatest circumference as compared with the other diameters, and the cranial fossae are less concave. The luetic type usually presents a considerably less general increase in size but due to the



FIG. 135. Localized pressure; small gumma

lack of development of the base we have as a result the so-called saddle nose.

It might be well in passing to mention briefly the various types and changes noted in the venous and arterial markings of the inner table. We are all familiar with the diploic circulatory channels as seen in the x-ray. The most striking veniplexus is, of course, the one situ-

ated in the posterior diploic system and which has often been noted as a stellate collection of channels. These venous channels are usually seen equally well on both sides of the skull but occasionally it has been noted in connection with underlying pathological lesions that local-

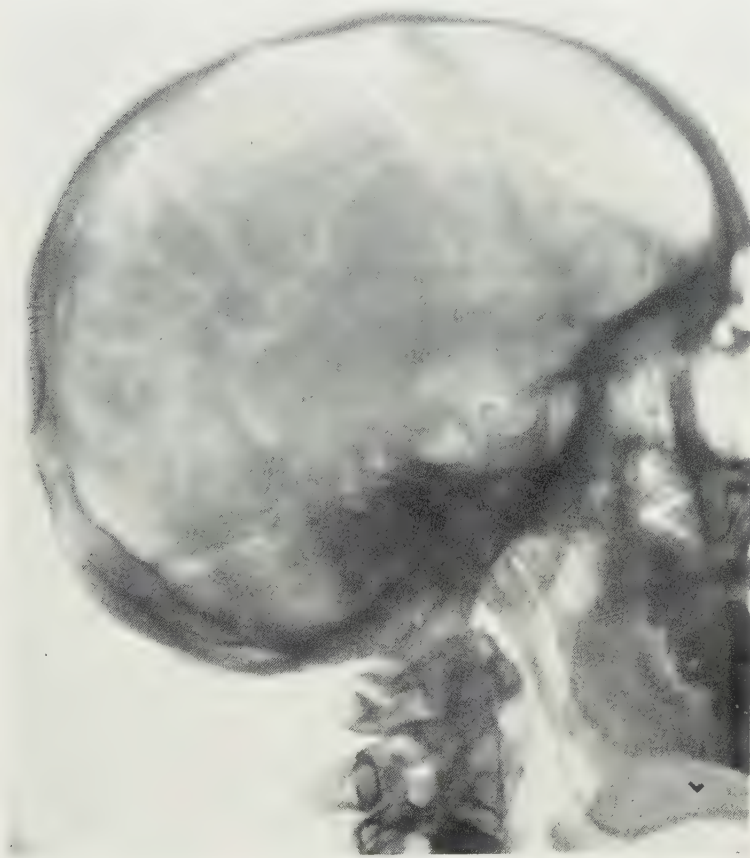


FIG. 136. Normal venous markings

ized areas will become more deeply grooved, evidently due to pressure or some disturbance in the circulation which has resulted in an engorgement of the veins in that vicinity, but without supporting clinical symptoms it would be hazardous to deduce from the x-ray alone

that there is underlying disease. It is often noted that the arterial channels, particularly the middle meningeal and its branches are considerably deeper than the average. This again, if bilateral, apparently means little or nothing; if unilateral it often is caused by what is evidently a localized pressure change in connection with one or more rather large pacchionian bodies which normally are found in the superior parieto-frontal region. Changes in the circulatory channels of course, occur slowly and their interpretation as an indication of disease must be done cautiously using them only as supporting evidence.

The changes due to localized pressure do not differ materially from those seen in generalized increased pressure except that it is localized to one particular area or areas as the case may be. As a rule localized pressure produces more of a change, because the pressure is more intense and therefore the atrophy is more profound. Of course, the changes seen in the bone vary with the part of the skull in question. The more delicate structures are destroyed before those of a more massive form. In examining local areas of pressure one must be careful to distinguish between atrophy and actual bone destruction. Of course, this is merely a difference in degree, not of kind, although when the bone is invaded by some neoplastic growth it produces a different appearance than simple atrophy from pressure. The bone shows more profound changes such as partial or complete loss of outline and what outline remains is of an extremely fuzzy, irregular appearance. Often the bone shows evidences of absorption and occasional attempts at regeneration. Simple atrophy from pressure does not show these changes. Bone infection will sometimes produce a condition comparable to atrophy but it is usually possible to differentiate, if not from the history at least from the depth and characteristics of the bony change.

Pressure is only one of the many things to be looked for in the x-ray examination of the skull. Its presence cannot be determined immediately after the pressure becomes a factor as it takes time to produce the bony changes which can be made visible in the x-ray film. The time necessary to produce these changes is of necessity decidedly variable, depending on the type and structure of the skull in question. It would, I believe, be pure guess work to try to make any definite statement as to the time necessary for these changes to occur, some skulls may show changes in a few weeks while others of more massive structure may well take months.

DISCUSSION

The following questions submitted to Dr. Schwartz before the Commission, together with the answers to them, are here reported verbatim.

DR. TAYLOR: Do you regard the x-ray as of definite value in the diagnosis of tumor? I should like to know how many cases you have diagnosed from the x-ray alone.

DR. SCHWARTZ: That is rather hard to answer definitely. I might say that the vast majority of x-ray evidence of tumors is of the indefinite type. That is the tumors we were able to localize absolutely are in the minority, unless they are of a calcified nature. Of course we have ventriculography, but I think we might say most of the evidence obtained is decidedly inferential, although sufficiently definite to arrive at a diagnosis of intracranial disease, and occasionally exact localization.

DR. HORRAX: May I add a word to Dr. Taylor's question? I think Dr. Schwartz has been rather too modest, because it seems to me the number of cases which are capable of diagnosis by x-ray are not the small minority which he has said because certainly in any large series of verified cases there are almost bound to be 20 per cent of pituitary adenomas, for instance, which are almost always capable of diagnosis by the x-ray. Then there are at least 10 or 12 per cent of meningiomas out of which probably a third will contribute information not only to the diagnosis of a brain tumor but also to the type of brain tumor. Furthermore, 80 per cent of supra-sellar cysts are diagnosable by the x-ray.

DR. SCHWARTZ: I think the percentages are just about right, but it is almost impossible to see tumors that are not close to the surface, unless they are calcified. The basal tumors, such as the pituitary, can be diagnosed with considerable accuracy as Dr. Horrax said. I rather thought Dr. Taylor had in mind those tumors more deeply seated in the brain, and that is what I had in mind when answering his question.

DR. TIMME: Dr. Schwartz, a great many children and young adults with a hypocalcemia show what is called "convolutional atrophy." Is there any method of determining by x-ray technique differences between that type of atrophy and atrophy due to intracranial pressure?

DR. SCHWARTZ: In the early stages, before the bone has become thoroughly organized, it is very difficult to differentiate between the two, but after a few years, or, in fact, often earlier than that, if the calcium situation becomes a little more normal, the bone immediately takes on a much more clear-cut appearance and then we have the convolutional digitations very clearly defined, as against the pressure type which blends into the surrounding bone and does not have the definition that the other type has, and besides in the type that you speak of the base does not show any evidence of distortion. Frequently in the pressure types we have a change in the basal angle or some change in the depth of the cranial fossae, but those are the only differential points that I think we can rely upon.

Section III

INCREASE OF INTRACRANIAL PRESSURE IN TUMORS AND
OTHER EXPANDING LESIONS OF THE BRAIN

CHAPTER XXIV

MECHANISM AND SYMPTOMS OF TUMORS OF THE THIRD VENTRICLE AND PINEAL BODY

WALTER E. DANDY, M.D.

TUMORS arising in and confined to the third ventricle for a long time give rise to no recognizable symptoms or signs except those of pressure. As the tumor grows beyond the confines of the ventricle or against contiguous areas of the brain signs and symptoms appear, namely, polyuria and polydipsia and visual disturbances when the region of the tuber cinereum and optic chiasm are involved. Other tumors arising in the third ventricle give the first neurological manifestations when they grow backward against the crural and midbrain causing difficulties of locomotion (often retro-pulsion) or when the nuclei of the third, fourth and sixth nerves lying in the midbrain just beneath the aqueduct of Sylvius are compressed through the intervening corpora quadrigemina. Pineal tumors likewise give no signs or symptoms of the tumor's location until the nuclei of the third nerve are compressed through the interposed corpora quadrigemina. The first objective evidence of compression of the oculomotor nucleus or nuclei is ptosis, either unilateral or bilateral. When ptosis is bilateral and without further involvement of the other muscular functions of the oculomotor nerves, the findings are practically pathognomonic of a tumor pressing down from the region of the corpora quadrigemina or pineal body.

Until ptosis develops tumors of the pineal body are likewise silent except for general pressure. Tumors of the third ventricle are therefore usually indistinguishable by signs and symptoms from tumors of the pineal body even after the tell-tale ptosis has appeared.

Tumors of the third ventricle, pineal body and midbrain give rise to intracranial pressure almost entirely owing to the hydrocephalus which results from occlusion of the ventricular channels. For this reason the tumors need be and usually are relatively very small—among the smallest causing symptoms of intracranial pressure, but because of the hydrocephalus the symptoms of intracranial pressure are usually most profound.

Tumors of the third ventricle occlude both foramina of Monro and therefore cause dilatation of both lateral ventricles but obliterate the third ventricle at least as a pathway for the transmission of cerebrospinal fluid into the fourth ventricle. Tumors of the pineal body and of the midbrain occlude the aqueduct of Sylvius and cause dilatation of both lateral ventricles and the third ventricle. However, pineal

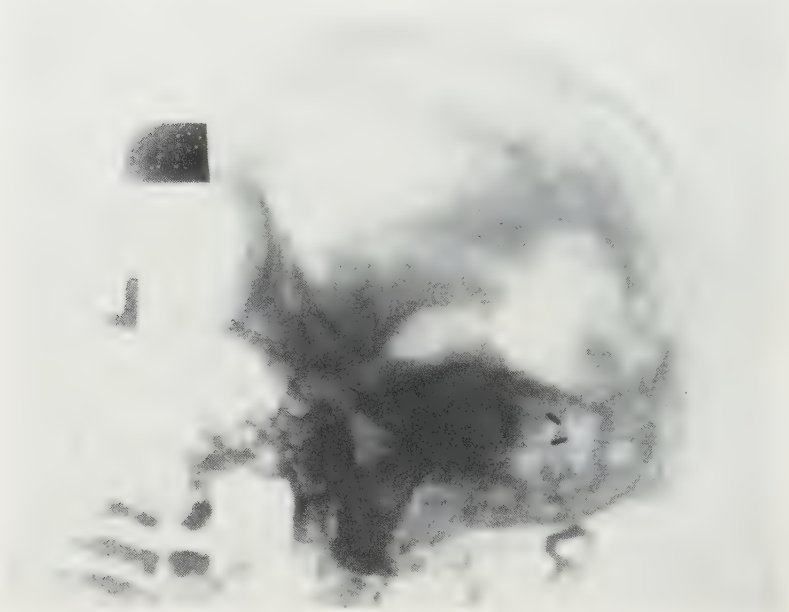


FIG. 137. Ventriculogram showing tremendous hydrocephalus from a tiny tumor in the third ventricle (fig. 141 (d)).

tumors may also grow anteriorly into and fill the third ventricle and even obliterate the foramina of Monro.

Fortunately the localization of tumors of the third ventricle and pineal body is now relatively simple by ventriculography. The ventricular changes induced by the tumor can be accurately demonstrated on the x-ray plates. There is no more characteristic finding in ventriculography. Since the foramen of Monro is blocked the air introduced into a lateral ventricle does not fill the third ventricle and does not cross to the other lateral ventricle. There is, therefore,

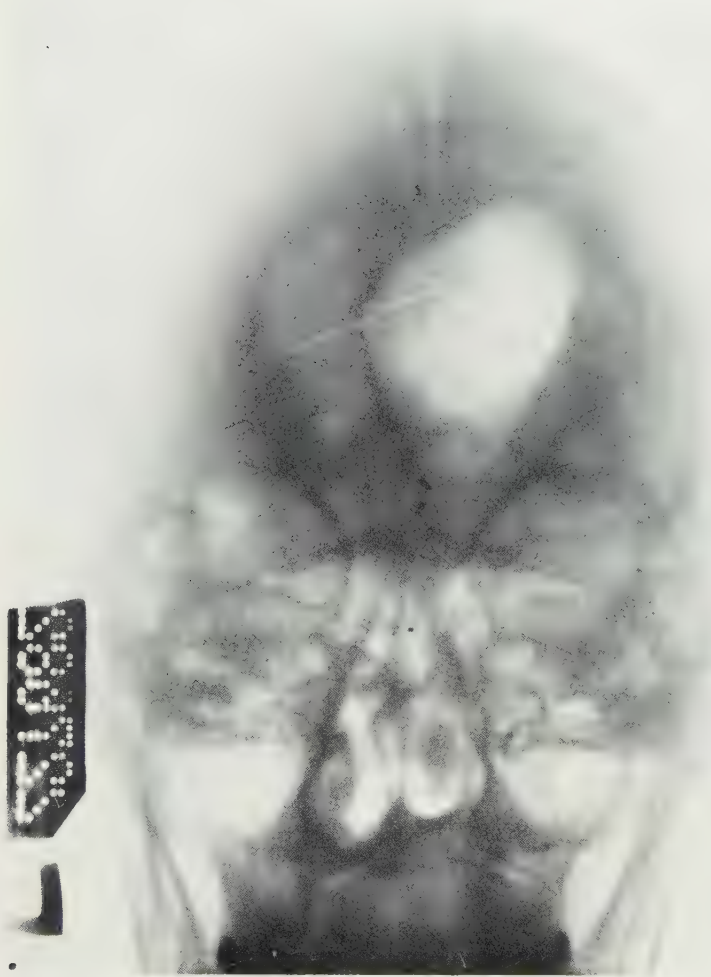


FIG. 138. Anteroposterior ventriculogram of patient whose lateral view is shown in figure 137. It will be seen that the ventricle is greatly enlarged; its angles all rounded and the ventricle is situated nearly in the center of the head. The shadow of the third ventricle is absent. If the opposite lateral ventricle were filled separately with air there would be an exact mere image of this ventricle and it also would cross the midline to the other side.

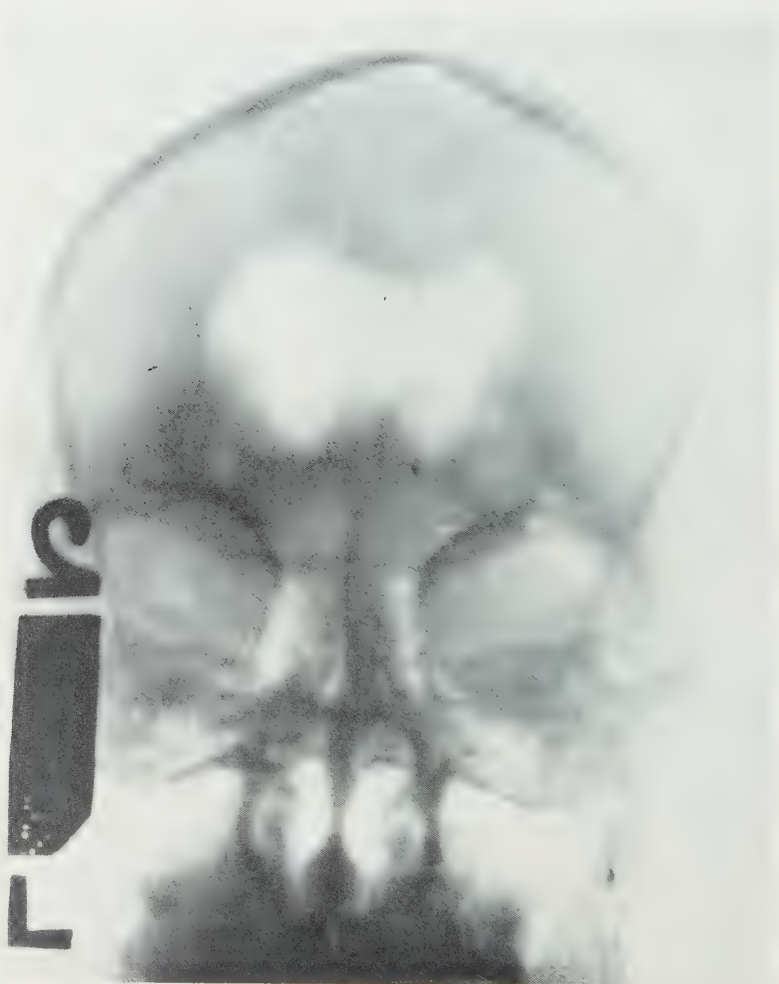


FIG. 139. Anteroposterior ventriculogram in which both ventricles have been filled with air. The seemingly confluence of the two ventricles is an important part of the picture. The septum lucidum shows a thin line bulging far over to the right; this indicates the absence of free communication between the two ventricles, and shows that there is more air in one ventricle than in the other. If the two ventricles communicated freely through the foramina of Monro this line would be strictly straight and vertical; the curved septum lucidum therefore indicates a third ventricle tumor. It will be noted that there is no shadow of the third ventricle.

present in the x-ray film a single dilated ventricle with its angles well rounded. The position of this lone ventricle is also characteristic in that it almost bisects the midline of the head. If the opposite lateral ventricle is injected at a subsequent sitting, precisely the same finding is obtained except that it is a minor image of the one on the opposite side. In neither injection has the third ventricle filled nor has the air

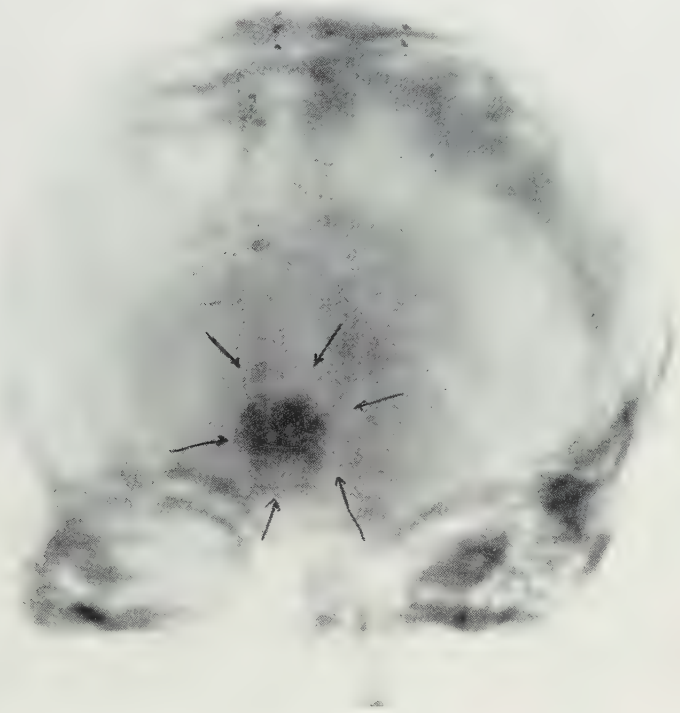


FIG. 140. Showing calcified pineal tumor—anteroposterior view.

passed out of the ventricle into the subarachnoid space. The only exit of the ventricle is occluded. If both lateral ventricles are separately injected or if air still remains in the first ventricle when the second is injected, one notes the striking absence of the third ventricle and a characteristic overlapping of the two lateral ventricles in the anteroposterior view. The septum lucidum also shows a character-

istic curve in the otherwise seemingly fused lateral ventricles (antero-posterior view). This thin septum should and would be straight if the pressure in the two lateral ventricles could be equalized by free intraventricular communication which is precluded by the closure of the foramina of Monro. It is, therefore, curved because there is

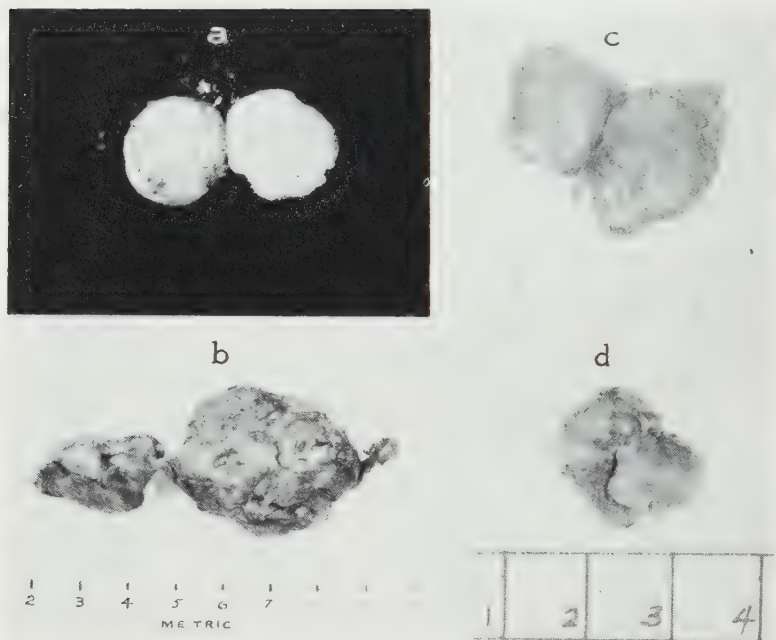


FIG. 141. (a) Tiny encapsulated fibroma removed from the third ventricle. This patient is living and well seven years after operation.

(b) Third ventricle tumor removed from patient shown in figure 142.

(c) Calcified third ventricle tumor laid open for mid section.

(d) Small tubercle successfully removed from third ventricle. This tumor in its gross aspect, size and position was similar to the tumor shown in (a).

somewhat more pressure in one side than in the other. It, of course, bulges into the ventricle having the less pressure.

The ventriculographic changes of pineal tumors differ in that both lateral ventricles are (at first) in free communication. As these tumors grow forward they encroach upon the third ventricle producing in the x-ray a filling defect. For such defects the lateral ventriculo-

grams are indispensable. One of the most important and most difficult intracranial differential localizations is between tumors at the aqueduct of Sylvius and those in the posterior cranial fossa. In the



FIG. 142. Post-operative photograph of patient whose tumor is shown in figure 141 (b). The incision for the operative approach is indicated by the arrows.

former there will be a filling defect of the third ventricle whereas in the latter not only is this absent but one can often see the shadow of the dilated iter and at times a dilated anterior portion of the fourth ventricle.

The size, shape, position or absence of the third ventricle are perhaps the most important data obtainable in ventriculography and nowhere is this information more necessary than in the localization of tumors in the midline of the brain.

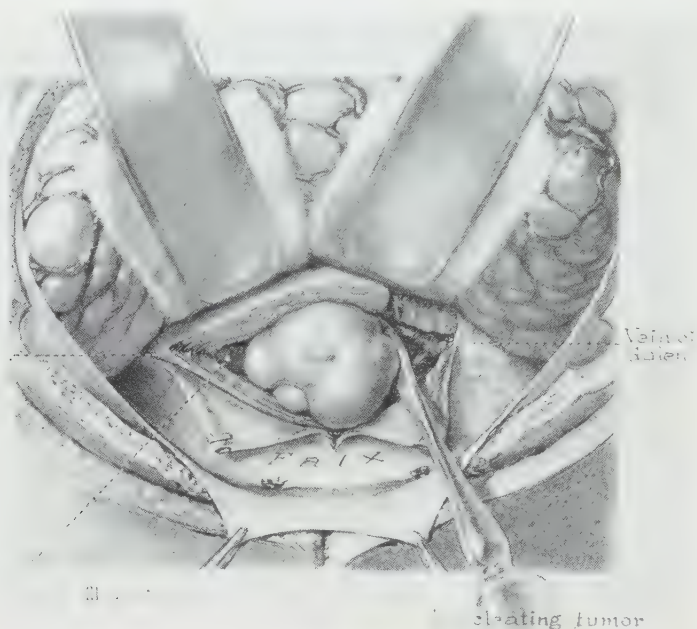


FIG. 143. Drawing to show the method of approach to tumors of the third ventricle, pineal and quadrigeminal bodies. The hemisphere is retracted from the falx after evacuating the fluid from the lateral ventricle. The corpus callosum is then split longitudinally and the third ventricle presents beneath. Many of these tumors lie between the veins of Galen, figure 141 (b) and (c). Others are situated more anteriorly figure 141 (a) and (d). In these cases it is necessary to enter the third ventricle after opening the lateral ventricle, following thence into the foramen of Monro with the chorioid plexus as a guide.

Special note should be made of one particular tumor in the third ventricle. We have recently had four cases all essentially similar in position, gross and microscopic appearance. They are apparently benign, well encapsulated, reddish brown, fairly firm tumors, and are attached to the superior wall of the lateral ventricle (ependymal tumors?) into which they seemingly drop and dangle. Because of

their benign character and encapsulation and apparently slow growth they act as a ball valve obstruction. In one of our cases in which a cerebellar operation was made for a presumed cerebellar growth there was entire absence of intracranial pressure at the time of operation and for weeks subsequently. The pressure then became fullblown in a few hours causing the cerebellar decompression to become full and tight. In the x-ray plate one of these tumors cast a dense shadow as large as a small walnut. At operation it was found to be completely calcified. We have had one other type of tumor in the third ventricle—a small round encapsulated hard fibrous nodule as large as a hazel nut. Histologically it contained no nuclear elements. It was successfully removed several years ago.

The treatment of these tumors is all dependent upon a precise localization and this is rarely obtainable without ventriculography. The injection of indigo-carmin into one large ventricle and its failure to cross to the other equally large ventricle (ventricular estimation) will often make the diagnosis correctly but there are too many possibilities of error to warrant its use to the exclusion of ventriculography. The operative approach for tumors of the third ventricle, pineal body, or corpora quadrigeminal bodies is by a posterior cerebral craniotomy approaching the midline of the head. A cerebral hemisphere (preferably the right) is then retracted from the falx (after evacuating the fluid in the corresponding lateral ventricle). The corpus callosum is split in the midline. The tumor is then usually seen between the two small veins of Galen and projecting backward to and behind the great vein of Galen. If a small tumor is situated anteriorly in the third ventricle the lateral and not the third ventricle will be opened when the corpus callosum is divided. By following the choroid plexus to the foramen of Monro, one can then safely split the margin of this foramen and the tumor will be immediately beneath. It is at times necessary to divide the tentorium to reach the posterior extension of the tumor around and back of the great vein of Galen. This dural incision is necessary in most pineal tumors and all growths of the corpora quadrigemina. Indeed many tumors in the anterior part of the cerebellum can be better reached by splitting the tentorium in this manner than by a subtentorial exposure. Three tumors have been successfully and totally removed from the third ventricle by this route. Section of the corpus callosum is often nearly complete but without obvious harmful effect.

DISCUSSION

The following questions, submitted to Dr. Dandy before the Commission, together with the answers to them, are here reported verbatim.

DR. STARR: After you have made a diagnosis of a tumor of the third ventricle do you consider the case hopeless, or do you attempt to operate, and if so, by what route?

DR. DANDY: An attempt is always made to remove them completely. Two of the patients shown in the lantern slides are living and well, one neoplasm was removed five years ago and the other two years ago.

DR. STARR: What route do you use through the hemisphere—from below or from above?

DR. DANDY: The route is through the corpus callosum which is split longitudinally. The tumors lie between and are attached to the two small veins of Galen and extends along the great vein of Galen.

DR. STARR: I would like to ask what the interval is between the injection of the ventricle with air and the actual operation. Do you delay the operation for some time after the use of the air, or do you go right on and operate immediately?

DR. DANDY: That depends upon the location of the tumor. The potential danger attached to the injection of air is greater in those cases having hydrocephalus because the air can not escape. If air can not escape, of course, it causes irritation of the brain and that induces further pressure. There are two ways of preventing all danger from the use of air. One is to remove it by ventricular puncture; another is to remove the tumor and automatically the air then reaches the subarachnoid space where fluid (and likewise air) is absorbed. If the ventricular spaces are open and the air can get into the subarachnoid space, the dangers of air are minimal. We do not fear air injections when the air can reach the subarachnoid space. In the presence of hydrocephalus we feel the sooner the tumor is removed and the air allowed to reach the subarachnoid space, the better and safer. Operation in those cases is therefore done very soon after the air injection.

DR. TIMME: May I ask Dr. Dandy whether the mere injection of this air into the ventricles is not done with a certain degree of danger? From his statement one would imagine that there was no danger connected with it.

DR. DANDY: We have lost one case in the last ten years, and that case was through an accident of my assistant who mistook the ventricle which was injected and tapped the wrong ventricle to release the air. I feel there is absolutely no danger in the use of air, if used properly. If it is not used properly, there is tre-

mendous danger. Without the air you can not possibly reach a diagnosis in these cases or in most others. With air you can make a diagnosis and a localization of every tumor in the brain which causes intracranial pressure.

DR. PENFIELD: Which positions do you find most useful in demonstrating the third ventricle, brow up, vertex up, or what position of the head?

DR. DANDY: We have to have both the brow up and the back up. If you do not have the back up, then you are not sure of your findings. They may be dependent purely upon the position and not on the tumor.

CHAPTER XXV

THE MECHANISM AND SYMPTOMS OF INCREASED INTRACRANIAL PRESSURE DUE TO ENCAPSULATED AND INFILTRATING TUMORS OF THE CEREBRAL HEMISPHERES¹

CHARLES H. FRAZIER, M.D., AND W. J. GARDNER, M.D.

THIS presentation will be in large measure an exposition of facts. We will not deal much in speculation and the facts have been collected solely from the clinical records and not from the experimental laboratory. For the purpose of this inquiry an arbitrary number—one hundred of verified pretentorial brain tumors were selected, variously distributed throughout the hemispheres. An attempt will be made to compare the effects of intracranial pressure especially in relation to five locations, occipital, temporal, parietal, frontal and motor cortex.

I. STATISTICAL

In our tabular study of these five groups certain criteria were selected as manifestations of pressure: Headache, vomiting, ventricular distention, papilloedema, brain hypertrophy. Distinction has been made as to the size of the tumor and as to whether it was within or without the brain mass, chiefly whether gliomata or encapsulated tumor.

When we come to consider the mechanism of increased intracranial pressure, there are certain factors quite obvious and indisputed: (1) increase in bulk caused (a) by the tumor; (b) by brain hypertrophy; (2) dilatation of the ventricles from ventricular obstruction. These no one will question and can be readily demonstrated by review of the findings either at operation or at autopsy. Other factors may be operative but not so easy of demonstration. I have in mind chiefly disturbances in the absorptive area or in the rate of secretion of cere-

¹From the Neurological Service of the Hospital of the University of Pennsylvania.

brospinal fluid. All these and other factors will receive consideration and be given their relative importance.

Cerebrospinal fluid pressure

In table XXII are the maximum, minimum and average cerebrospinal fluid pressures in the several groups of tumors, measured in terms of millimeters of mercury. Evidently there is not a wide variation in the average, from 19 to 26; the highest maximal pressure, 60, was observed in a frontal lobe tumor and the low maximal 35 in a temporal lobe tumor, the sequence from high to low being frontal, parietal, occipital, motor cortex and temporal lobe. Naturally many variable factors come into play which cannot be defined in every instance from information obtained on the operating table. In the subcortical tumor one may be uncertain as to its exact dimensions. The dimension of the tumor if always known would make

TABLE XXII

	OCCIPITAL	TEMPORAL	PARIETAL	FRONTAL	MOTOR CORTEX
Maximum.....	44	35	50	60	42
Minimum.....	12	10	8	7	9
Average.....	26	22	19	24	20

this comparative study exact, but as this could not always be determined on the operating table and is not always specified in autopsy reports, of necessity, we must be content to make comparison on the basis of averages in the variously localized lesions. Of the other factors often undetermined is the exact location of the growth with relation to the ventricles.

Size of tumor

One might infer that the size of the tumor would have a very considerable influence upon the pressure phenomena. A chart (fig. 144) was prepared from a series of tumors, the cubic contents of which were known. As a yardstick of the amount of pressure, the degree of papilloedema in terms of diopters was taken. In this chart it may be seen that with certain exceptions the degree of pressure did not increase proportionately with the size of the tumor. To be sure

the tumors in this series were encapsulated tumors without the cerebral mass, but if any conclusion from this comparison were admissible, it would be this: that factors other than tumor bulk are equally if not more responsible for the increase of intracranial pressure, such, for example, as hypertrophy of the cerebral hemispheres and dilatation of the ventricles.

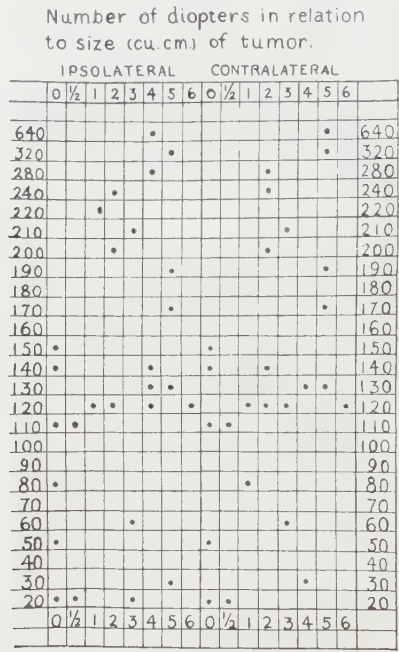


FIG. 144. This chart graphically represents the comparison of the volume or bulk of the tumor to the number of diopters of papilloedema. Each case is represented by a dot. On the lateral margins is the scale of cubic centimeters of tumor mass, on the margins, top and bottom, is the scale of diopters from 0 to 6.

Papilloedema

We have consolidated the figures representing the elevation of the discs in diopters for the two general tumor groups in the several locations. The degree of papilloedema in most instances at least must be proportionate to the degree of intracranial tension. Taking as we have for comparison maximum and average measurements there is a

striking similarity between the encapsulated and non-encapsulated tumor as well as between the tumor of different localities. Frequently has the statement been made that the signs of increased pressure are neither so constant, nor the degree of pressure so high in frontal lobe tumors as in those of the parietal and occipital lobes. Table XXIII does not bear this out, nor do the figures in other tables show any striking difference as to evidences of pressure between tumors of frontal and those of other lobes. If any comparison is to be made between degrees of papilloedema in encapsulated and non-encapsulated tumors it will record a very trivial difference: the degree of

TABLE XXIII

	OCCIPITAL		TEMPORAL		PARIETAL		FRONTAL		MOTOR CORTEX	
	Maximum	Average	Maximum	Average	Maximum	Average	Maximum	Average	Maximum	Average
PAPILLOEDEMA—GLIOMATA										
I.....	6.5	3.3	6	3	7	$1\frac{3}{4}$	6	2.8	6	2.6
C.....	7	3.1	8	3	6	2	6	2.9	6	2.7
PAPILLOEDEMA—ENCAPSULATED TUMORS										
I.....	5	3	6	2	7	$2\frac{2}{3}$	6	2.6	5.5	1.3
C.....	5	3	6	$1\frac{1}{4}$	6	2	6	2.5	5.5	1.3

The figures represent diopters in elevation of discs. "I" represents ipsilateral or side of tumor and "C" contralateral or opposite side. There is one column for gliomata and one for encapsulated tumors. There are five general subdivisions for the occipital, temporal, parietal, frontal and motor cortex locations.

choking in encapsulated tumors both as to maximum and average if not equal to is slightly lower than the figures for the non-encapsulated growths.

X-ray evidence

The roentgenogram may be taken as another indication of the degree of pressure but naturally the time factor—the duration of the lesion—plays an important part. Table XXIV displays the figures of the evidence of pressure revealed in the roentgenogram. In the entire series there was evidence of pressure as indicated by convolutional

markings or by atrophy of the clinoid processes and dorsum sella, in 54 per cent of the endotheliomata and 34 per cent of the gliomata. In only two cases, both calcified endotheliomata of the motor cortex, was there x-ray evidence of pressure in the absence of any clinical evidence of increased intracranial pressure.

As was anticipated the time factor was influential. There was always x-ray evidence of pressure when the lesions were of fifteen months' duration and there was no x-ray evidence of pressure when the lesion was of only five months' duration. One must admit that

TABLE XXIV
X-RAY EVIDENCE OF PRESSURE

	ENCAPSULATED TUMORS	GLIOMATA	BOTH
<i>(Average spinal fluid pressure—millimeter of Hg.)</i>			
With x-ray evidence of pressure.....	24.8	24.0	24.3
Without x-ray evidence of pressure.....	18.2	23.8	22.4
<i>Average duration of pressure—months</i>			
With x-ray evidence of pressure.....	13.2	17.7	15.3
Without x-ray evidence of pressure.....	9.0	3.3	5.4
<i>Average papilloedema—diopters</i>			
With x-ray evidence of pressure.....	3.1	3.5	3.3
Without x-ray evidence of pressure.....	1.7	2.3	2.1

the precise duration of the lesion is more or less uncertain, as there may have been no apparent symptoms for a variable time after the tumor first began to grow. The duration of the lesion obviously could be determined only from the patient's history.

The evidence of pressure, as indicated by degrees of choking, correspond somewhat to the presence or absence of x-ray evidence. Thus in table XXIV it will be seen that the average elevation of the discs in those *with* x-ray evidence of pressure was 3.3 as compared with 2.1 of those *without*.

Hemispheric hypertrophy

We have had the conviction that hypertrophy of the hemisphere in which the tumor was situated, to which condition Spiller first called attention, is an influential factor in the mechanism of increased intracranial pressure. This statement would apply only or chiefly to infiltrating tumors within the cerebral mass—the gliomata. To be sure opportunities for observation of this phenomenon can be had only at autopsy, and as only an occasional fatality would be found in the endothelioma series, the evidence at hand has been taken from the series of gliomata. In the latter in every instance, when in the autopsy record the observation is recorded, there was a demonstrable hypertrophy. This it seems to us is one of the conspicuous

TABLE XXV

	GLIOMATA	ENCAPSULATED TUMORS	TOTAL
Ipsilateral collapse.....	19	12	31
Ipsilateral dilatation.....	2	0	2
Contralateral collapse.....	8	4	12
Contralateral dilatation.....	9	5	14
Contralateral normal.....	4	1	5

Limited number of observations in a series of 100 pretentorial brain tumors as to ventricular collapse or dilatation, ipsilateral or contralateral.

findings in this study of the mechanism of pressure. It will be conceded, we take it, that the size of the glioma may have little effect on pressure conditions, since in its advancing growth, the glioma destroys the normal brain tissue in its immediate location. But the hypertrophy of the uninvaded portion of the hemisphere, present as recorded in 100 per cent of the observations, is a factor that must be given its proper evaluation. In contrast to this universal finding in gliomata we found the record of only two cases of endotheliomata, in which there was said to have been moderate hypertrophy of the hemisphere on the affected side.

Lateral ventricles

The condition of the ventricles, whether collapsed or dilated, must be accepted as of importance in any consideration of the causes of in-

creased intracranial pressure. Were ventriculograms made in every case, we would have very exact information. But inasmuch as in only the minority have we had resort to ventriculograms, our knowledge as to whether the ventricles were dilated or not could be derived only from the result of ventricular puncture. We are further restricted in the scope of observations in that ventricular puncture (1) was not made in every case, (2) in most instances was made at the operation only on the side of the tumor, (3) may have failed to find the ventricle. In this total series of 100 cases the two significant facts of the ventricular studies were these: in only two cases was ipsilateral dilatation of the ventricles recorded and in thirty-one cases it is recorded that there was ipsilateral collapse. There were fourteen cases in which contralateral dilatation was recorded and twelve cases in which there was contralateral collapse.

Headache and vomiting

It is perfectly proper, we take it, to include headache and vomiting as indices of increased intracranial pressure. Table XXVI records the relative frequency of both headache and vomiting in each of the five localities. A mere glance at the table shows incidentally that headache is a much more constant phenomenon than vomiting in the proportion of 91 per cent for headache and 59 per cent for vomiting. Note the total average for tumors of all localities (table XXVI). In comparing the percentages of one location with another, one is struck with the relatively low figures of the parietal lobe tumors. The significance of this with regard to the mechanism of pressure is certainly not apparent. One might have thought that the nearer the tumor to the pacchionian bodies, as the recognized avenues of absorption of cerebrospinal fluid, the greater the pressure effects and as the parietal lobe tumor is in closer relation than the tumors of other lobes to these bodies, we would have expected a relatively higher percentage of headache and vomiting. The figures, however, do not bear out this contention. Nor is there enough difference between the percentages of the encapsulated to the non-encapsulated tumors of the various lobes to justify conclusions. In the parallel columns of table XXVI it will be seen that there is not a striking difference between the percentages of the two tumor types. What difference there is, however, points to higher percentages in the non-encapsulated groups in three

localities, frontal, occipital and motor cortex. In other words some factor other than the size of the tumor or its location causes a higher percentage of headache and vomiting in the non-encapsulated growth. In all probability this factor may be hypertrophy of the hemisphere, which, as previously noted, is an almost constant accompaniment of the infiltrating glioma. This table records in percentages the relative frequency of headache and vomiting in (1) the gliomata (2) the non-encapsulated tumors of the several lobes.

TABLE XXVI

	OCCIPITAL	TEMPORAL	PARIETAL	FRONTAL	MOTOR CORTEX
HEADACHE					
	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
Gliomata.....	100	95	72	100	91
Encapsulated tumors.....	90	100	77	90	88
Average percentage for all locations					
Gliomata.....	93.0				
Encapsulated tumors.....	88.0				
VOMITING					
Gliomata.....	85	56	45	63	81
Encapsulated tumors.....	60	75	33	50	28
Average percentage for all locations					
Gliomata.....	66.0				
Encapsulated tumors.....	49.1				

II. PHYSIOLOGICAL

In the first part of this review, dealing with the mechanism of intracranial pressure as it pertains to pretentorial tumors, we have presented in statistical form the facts that have been garnered from a series of 100 verified tumors, situated in one of five designated locations. From these statistics as indices of the presence or the degree of pressure, we have arbitrarily chosen (1) the x-ray evidence of structural alterations in the skull, (2) papilloedema, (3) cerebrospinal

fluid pressure, as recorded with the mercury manometer, (4) headache and vomiting, and (5) the size of the tumor. From these different angles, we may draw these preliminary conclusions:

1. The degree of intracranial pressure is not in direct ratio to the size of the tumor.

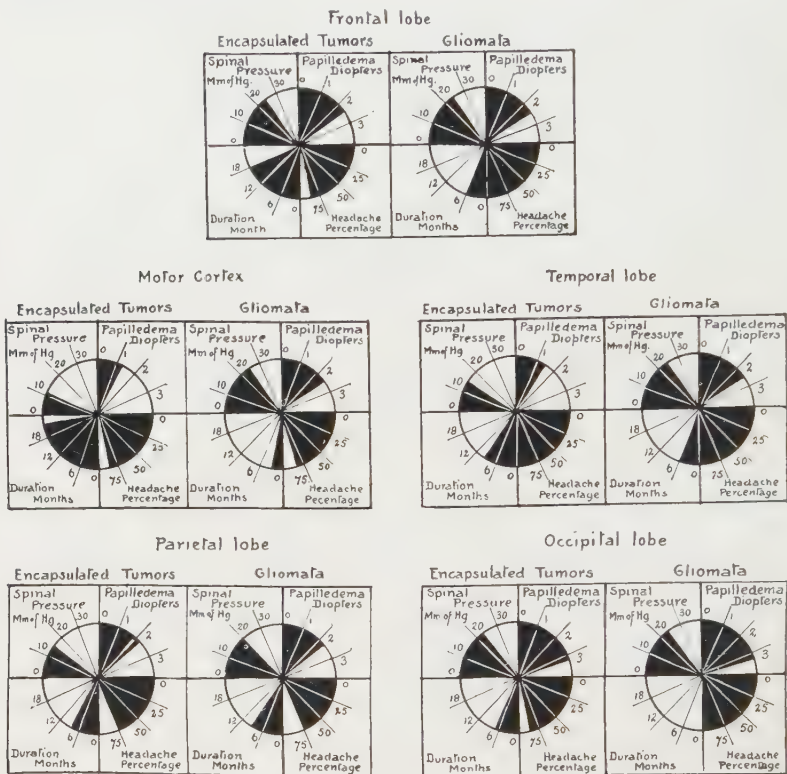


FIG. 145. Graphic representation of the relation of spinal pressure, papilloedema, headache and duration of pressure symptoms in the two groups of tumors in the five different locations.

2. The degree of intracranial pressure bears no relation to the site of the tumor, whether in the frontal, parietal, temporal, occipital lobes, or in the motor cortex.

3. There is reason to believe that in the gliomata hypertrophy of the hemisphere is an almost constant factor.

There remain to be discussed two very essential questions; first, what may disturb the absorption of the cerebrospinal fluid and, secondly, what may disturb the production of cerebrospinal fluid. These are questions altogether inseparable from a discussion that concerns the mechanism of increased intracranial pressure and while we have delved patiently into the possible influences of other physical factors, we ultimately and inevitably must face these two essential factors, factors that concern the fluid rather than the solid content of the cranial cavity, namely, the rate of absorption and the rate of production.

We cannot discuss the question of fluid secretion or fluid absorption without at least a brief reference to the physiological processes. While at one time, influenced by our own experimentists² and the experiments of others, we were wont to favor the secretory theory of cerebrospinal fluid production, the accumulative evidence of recent years supports the theory that the cerebrospinal fluid, as the aqueous humor of the eye, is a product of dialysis, a transudate; on the one hand we have production by filtration from the capillary bed of the choroid plexus, on the other absorption into the venous channels. (Pacchionian bodies and longitudinal sinuses.) By artificial changes in the relation of venous to cerebrospinal pressure the normal current within the lateral ventricle may be reversed. Accepting this theory as to the origin of the cerebrospinal fluid, we should also acknowledge that the rate of absorption and, at least for the sake of argument, the production of cerebrospinal fluid, have a direct relation to venous pressure.

Consider first the question of the rate of production of cerebrospinal fluid in brain tumors. Whatever the mechanism, we are convinced that in certain instances the rate of production is abnormally and excessively high. We might cite instances of the rapid refilling of the ventricles (within a few hours) after the withdrawal of fluid. In one instance it is recorded that within two hours of the withdrawal of 75 cc. the pressure of the cerebral hernia at the site of the decompression was as marked as before the fluid withdrawal.

While this phenomenon itself, excessive production of cerebrospinal fluid, will be accepted by neurosurgeons generally, as admitting of no dispute, there may be some difference of opinion as to the mechanism.

² Frazier, C. H., and Peet, M. M.: Factors of influence in the origin and circulation of the cerebrospinal fluid. *Am. J. Physiol.*, 1914, xxxv, 268.

According to Stopford³ excessive production is the result of pressure on the veins of Galen and he has demonstrated in the anatomical room how these veins are so situated that they may be readily compressed against the splenium of the corpus callosum, either indirectly or directly, by tumors especially those of the posterior rather than the anterior portions of the hemispheres. The theory seems plausible.

There has always been in our minds the presentiment that in brain tumors a vicious circle is established. Whether the loss in equilibrium between production and absorption be due to excess in production or delay in absorption, to one or both, is a matter largely of speculative interest.

We have already referred to hyper-production. What about delayed absorption. If it be true that the rate of absorption is influenced altogether by conditions of venous pressure, is it not reasonable to assume that the increase in intracranial pressure caused by the tumor itself will begin to cause venous congestion and increase of venous pressure, and, as the venous pressure increases, the rate of absorption of cerebrospinal fluid is delayed. Thus a vicious circle is established, delay in absorption causes increase in fluid, increase in fluid causes a rise in intracranial pressure, increase in intracranial pressure causes an increase in venous pressure and an increase in venous pressure causes delay in absorption. Thus the cycle is completed. This seems almost too apparent to admit of discussion. If accepted we need look no further for what the writers believe to be the predominant physical forces in the mechanism of increased intracranial pressure, namely hyper-production and delayed absorption.

GENERAL CONCLUSIONS

1. The size of the tumor is not proportionate to the degree of intracranial pressure.
2. The site of the tumor seems to have little or no influence upon the degree of pressure.
3. Hypertrophy of the hemisphere is an almost constant and no doubt a factor in the production of increased intracranial pressure.
4. The most important factors in the production of increased intracranial pressure and the pressure of pretentorial tumors are (a) hyper-production of cerebrospinal fluid, and (b) delayed absorption of cerebrospinal fluid.

³ Stopford, J. S. B.: The causation of the increased intracranial pressure associated with tumours within the cranium. *Brit. Med. J.*, 1926, ii, 1207.

CHAPTER XXVI

INTRACRANIAL PRESSURE IN TUMORS AND OTHER LESIONS OF THE HYPOPHYSIS AND PITUITARY REGIONS

MAX M. PEET, M.D.

THE evidences of pressure produced by tumors of the pituitary and pituitary region may be either local, general, or a combination of the two, one or the other, however, generally predominating. Strictly intrasellar tumors as a rule cause local signs and symptoms for a considerable period before manifesting any general pressure phenomenon. Not infrequently these tumors show only local pressure symptoms throughout the course of the disease. Tumors in the region of the pituitary, but not intrasellar in origin, may show either local or general pressure manifestations, depending largely upon the anatomical location of the new growth. Local signs generally predominate and may alone be present if the tumor is situated in front of or to one side of the sella turcica. On the other hand suprasellar tumors, because of their intimate relation to the third ventricle and foramina of Monro frequently show general pressure symptoms comparatively early. Occasionally such a tumor gives evidence of no local pressure.

The signs of local pressure are shown by the x-ray, ocular fundus, and visual field examinations. The symptoms are referable to pressure on adjacent structures; visual impairment from direct involvement of the optic nerves; headache, usually ascribed to capsular distention; and physiological or gross body changes associated with hypopituitarism.

The x-ray findings are almost pathognomonic. In early cases the sella turcica shows simple enlargement with thinning of its floor. As the pressure continues the posterior clinoid processes gradually lose their lime salts and all x-ray evidence of the dorsum sella eventually disappears. Coincident with the destruction of the posterior clinoid processes or at a later period a shortening and finally a disappearance of the anterior processes occurs (fig. 146). The posterior clinoids

being usually much lighter architecturally, almost always show the greater destruction. The sella floor then shows erosion and in advanced cases actual perforation. Usually both the vertical and the antero-posterior diameter of the sella turcica are definitely increased (fig. 147), although occasionally only the latter is noticeable. The posterior clinoid processes are not actually destroyed in every case in which they do not cast an x-ray shadow, as was shown by a postoper-

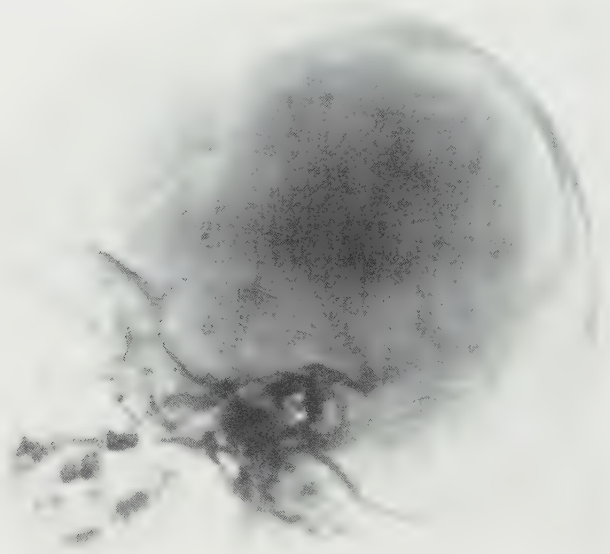


FIG. 146. Enormous enlargement of the sella turcica in a girl four years old. The anterior and posterior clinoid processes are completely destroyed, only the base of the dorsum sella remaining. The shadow suggesting the anterior processes is in reality the curved edge of the great wing of the sphenoid. Contrary to the usual findings in children, this sellar enlargement was due to a solid tumor.

ative series of x-rays taken over a long period. After several months a faint outline of the dorsum sella could be seen and eventually the lime salts were almost completely restored, the dorsum sella appearing thinner than usual, but otherwise normal in size and position.

Tumors within the sella, but on the upper surface of the hypophysis sometimes produce partial or complete destruction of the posterior clinoid processes without other enlargement of the sella and without

thinning of its floor. Very early pressure may show simply as a thinning of the midportion of the dorsum sellae, the upper persisting as a cap (fig. 148). In some comparatively early cases the roentgenogram shows the thinned dorsum sellae as a nearly vertical line, the clinoids having been pushed upward or even tilted slightly backward. This

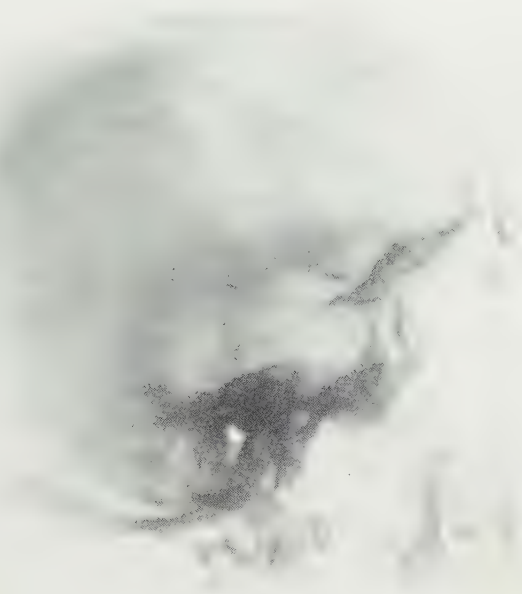


FIG. 147. General enlargement of the sella turcica by a pituitary adenoma. The posterior clinoid processes are practically destroyed and the anterior processes show pressure atrophy. The sellar floor is indistinct from erosion. There had been left homonymous hemianopsia for at least four years.

picture in our experience is suggestive of an intrasellar cyst rather than a solid tumor, although it may occur with either.

Further indication of a cyst, although not direct evidence of any pressure, is an area of calcification, often crescentic in outline, usually above, but often extending into the sella (fig. 149). Somewhat similar calcifications are occasionally seen in a suprasellar endothelioma, in the wall of the internal carotid artery, and in the partially calcified wall of an aneurism. These have been mistaken for calci-

fication in a pituitary or a Rathke's pouch cyst. However, endotheliomas in this region are comparatively rare and calcification in them unusual. There is also little likelihood that the lime salts will be deposited in a crescentic manner. Calcified cysts are much more commonly visualized by the x-ray than calcification in the wall of the

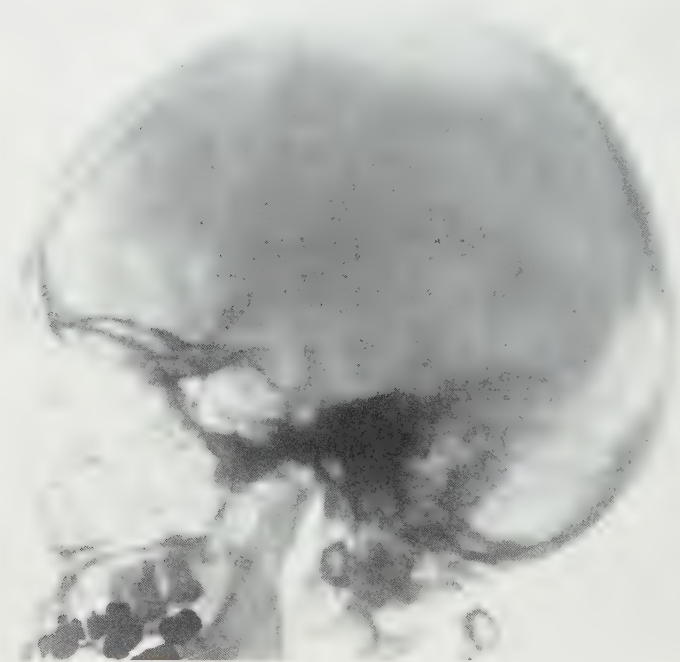


FIG. 148. Thinning of the mid portion of the dorsum sella, the upper portion persisting as a cap. The anterior clinoid processes are normal as is the floor and the sella is not enlarged. An adenoma on the upper surface of the hypophysis producing marked visual loss was found. The patient, though obese, still menstruated.

internal carotid artery or in aneurisms. In both the latter conditions the calcification may assume a crescentic outline, but in neither have we seen the typical enlargement of the sella turcica or destruction of the posterior clinoid processes. Theoretically the latter might occur with an aneurism, but its presence should be easily detected by the

bruit heard on auscultation, the throbbing, roaring noise complained of by the patient, and the frequently associated exophthalmos, cranial nerve palsies and orbital venous congestion.

The x-ray negative should be perfect from the technical standpoint, since otherwise, early changes in the posterior clinoid processes and small calcareous deposits might easily be obscured. In addition to the detail film of the sella and the usual lateral stereoscopic views we have

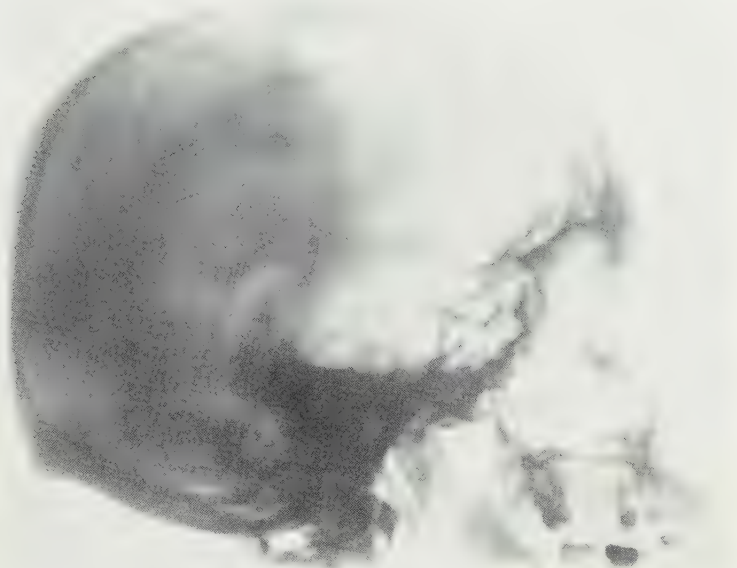


FIG. 149. Suprasellar calcification extending slightly into the sella, typical of a Rathke's pouch cyst, although in this case occurring in a pituitary adamantinoma. The anterior and posterior clinoid processes have disappeared. The patient was a girl of ten years.

found valuable evidence in films taken in an anterior-posterior position, the rays so directed that the posterior clinoid processes are seen through the foramen magnum. The location of calcium deposits in a cyst wall are clearly shown by this method (fig. 150).

A differential diagnosis must be made between tumors of the pituitary and pituitary region (suprasellar) and tumors situated in other locations since some of the latter produce changes in the sella

and clinoid processes closely resembling those usually identified with the former. In cases of cerebellar tumor we have seen enlargement of the sella turcica comparable to that produced by a moderate sized hypophyseal adenoma (fig. 151). In the former, however, the enlargement is uniform, the outlines are clear cut, and the posterior

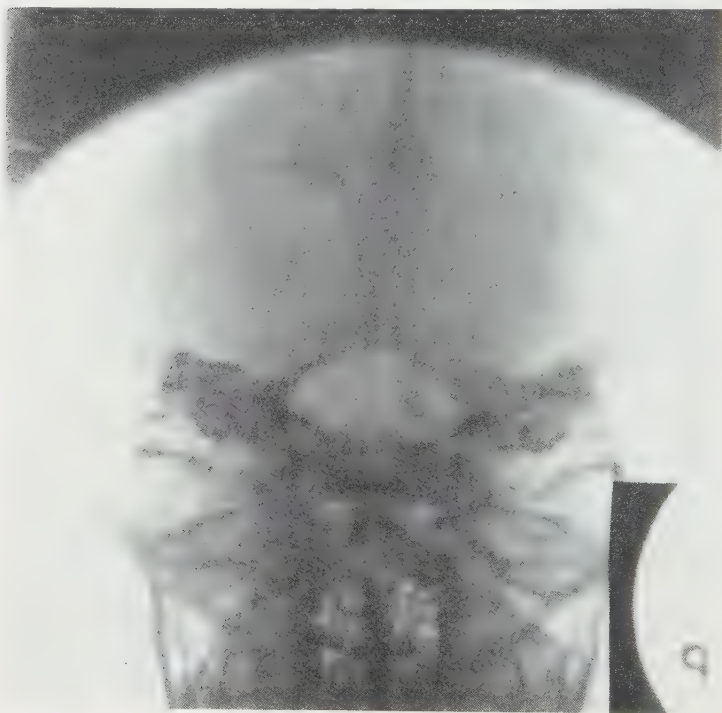


FIG. 150. Anteroposterior roentgenogram, the rays directed so that the clinoid processes are viewed through the foramen magnum. Calcification can be seen in the right wall of a sellar and suprasellar craniopharyngeal duct cyst. The patient was a girl of six years.

clinoid processes, although perhaps thinned, are usually not destroyed and retain sufficient calcification to stand out sharply. The sellar floor may appear very thin, but no erosion is evident and here also sufficient calcium is retained to assure a sharp outline. These sellar changes are generally attributed to the downward pressure of a distended third ventricle, a part of the hydrocephalic condition always

present in cerebellar tumors giving the above picture. Under these circumstances the adult sella is usually deep and well rounded, but in children, especially those with prolonged intracranial pressure, the sella may be quite shallow, corresponding to the general flattening of the base of the skull. The differential evidence afforded by the x-ray is particularly important in these cases, since cerebellar lesions

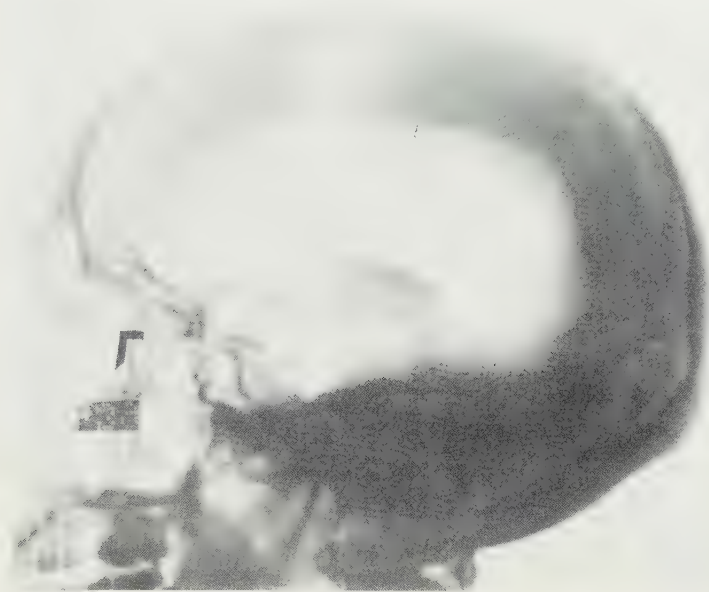


FIG. 151. Ventriculogram of a case of cerebellar tumor. The sella turcica shows enlargement comparable to that produced by a pituitary adenoma. The posterior clinoid processes are here much atrophied, although in many cerebellar cases they stand out clearly. The sellar floor shows no thinning. Marked dilation of the lateral and third ventricles is shown.

occasionally simulate a pituitary tumor with hypopituitarism, and conversely, as pointed out by Bailey (1), cerebellar symptoms may be produced by suprasellar tumors.

Changes in the clinoid processes and sella turcica suggestive of pituitary tumor have also been noted in tumor of the Gasserian ganglion, of the frontal lobe, of the parietal lobe and of the acoustic nerve. A Gasserian ganglion tumor had produced an enormous enlargement of

the sella turcica, but the outlines remained clear and sharply drawn. No evidence of hydrocephalus was present and we believe the changes noted were the result of direct lateral pressure by the adjacent tumor (fig. 152). A somewhat similar enlargement was noted in a patient having an enormous cholesteatoma of the left frontal lobe (fig. 153). No visual changes were present. Gliomas of the frontal lobe have

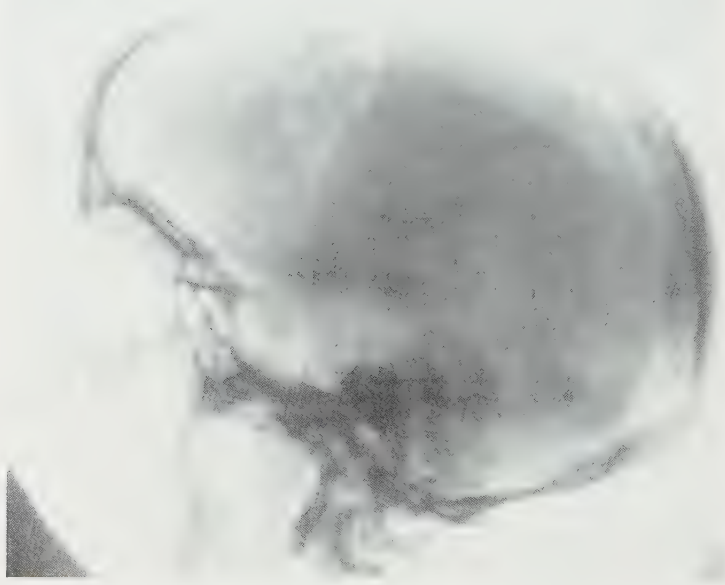


FIG. 152. Enlargement of the sella turcica by lateral pressure. The floor is irregular, but sharply outlined, as are the anterior clinoid processes. A large tumor of the gasserian ganglion was removed at operation.

caused somewhat less enlargement of the sella turcica, probably because they had been present for a much shorter period.

A rather marked enlargement of the sella turcica resulting elsewhere in a diagnosis of pituitary tumor, was present in a patient found to have a large ependymal cyst of the right parietal region (fig. 154). It was evident from the nature of the lesion that slight pressure had been exerted for many years. Endotheliomas in the parietal and posterior parietal regions produced suggestive enlargement of the sella turcica. However, the sellar outline was usually very sharp, at

once casting doubt as to the presence of a pituitary tumor, though in one case the posterior clinoids had been practically destroyed, (fig. 155). Cushing (2) has also described a case of sellar distension with anosmia due to a parietal endothelioma. We have had two cases of acoustic tumor in which the posterior clinoid processes were largely destroyed. In both a prolongation of the tumor in front of the pons

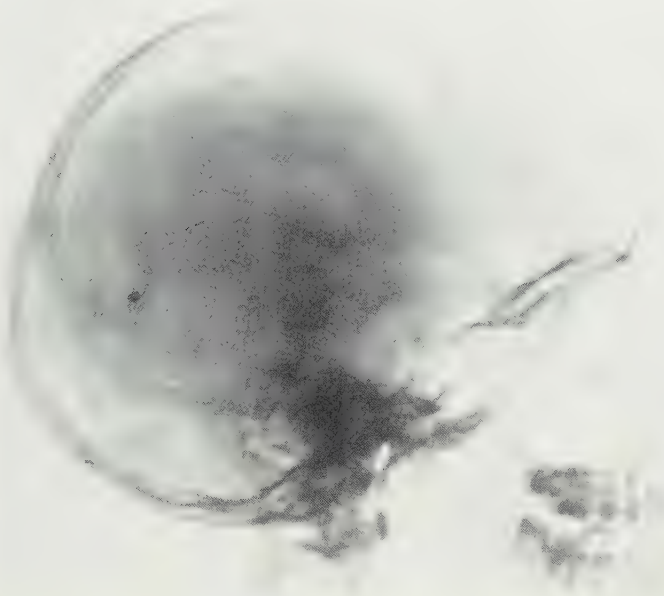


FIG. 153. Distention of the sella turcica by pressure from above. A large cholesteatoma of the left frontal lobe had pushed the brain into the sella turcica, causing a marked enlargement and thinning of the posterior clinoid processes. The sellar outlines, however, are sharp. No visual field defects were present.

with resulting direct pressure against the dorsum sella was found at operation.

It is therefore evident that tumors on either side, or above, or behind the sella turcica, and subtentorial tumors associated with hydrocephalus, may produce changes in the sella or in the posterior clinoids alone, which are highly suggestive of pressure from tumors of the pituitary or pituitary region.

Second in importance to the x-ray evidences of local pressure are the changes in the visual fields, second only in that they usually appear at a later stage. To the patient the visual loss is of first magnitude and it is generally the symptom for which he seeks medical attention. In fact, not infrequently, the physicians first intimation of a pituitary tumor is the characteristic change in the visual fields. These changes

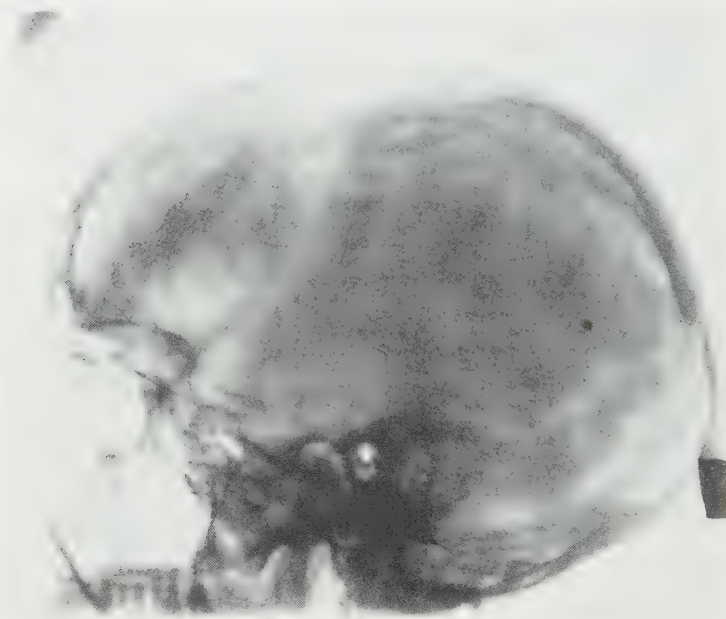


FIG. 154. Enlargement of the sella turcica with destruction of the posterior clinoid processes by an endymal cyst in the right parietal region.

have been so thoroughly described that they are given here only for the sake of completeness.

Pressure on the optic nerves and chiasm from tumors or cysts originating within the sella produce bitemporal or homonymous hemianopsia, depending on the direction of their upward growth. If the pressure is first directed against the chiasm a typical bitemporal hemianopsia results (fig. 156). A tumor rising in the midline may produce the same field defects even though the chiasm is not involved, since pressure will be exerted on the crossed fibers as they lie on the inner side of

each optic nerve. However, as pointed out by Walker and Cushing (3, 4) bitemporal hemianopsia is most often due to tension with resulting strangulation of the crossed fibers in the chiasm.

Since the fibers from the lower half of the retina occupy the lower portion of the optic nerves, upward pressure of an intrasellar tumor against their median-inferior aspect will result in an upper quadrant visual field defect before a hemianopsia develops. If the pressure or

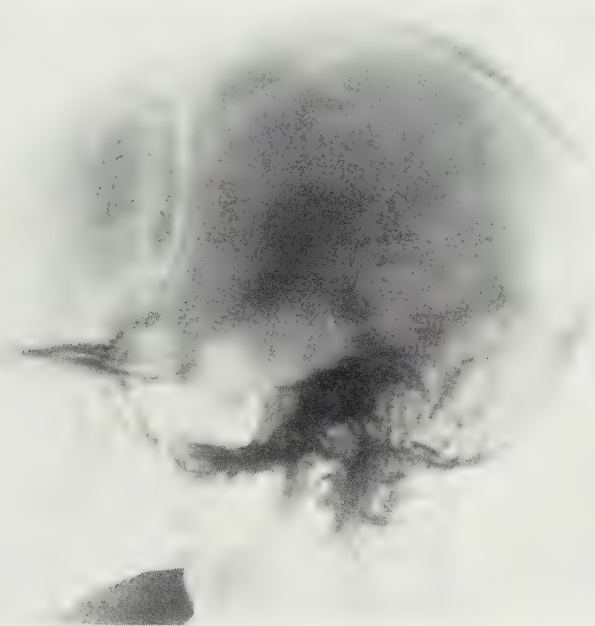


FIG. 155. Enlargement of the sella turcica with thinning of its floor and partial destruction of the posterior clinoid processes by an endothelioma in the left parietal region.

tension has been equal on both nerves the upper quadrant in each temporal field will be destroyed (fig. 157). The color fields disappear before the form fields are seriously contracted. A tentative diagnosis may be made even before quadrant defects appear, as the earliest manifestations of pressure may be an upper bitemporal slant, a finding especially emphasized by Cushing (4) (fig. 158).

Frequently a hypophyseal tumor grows more rapidly on the right or

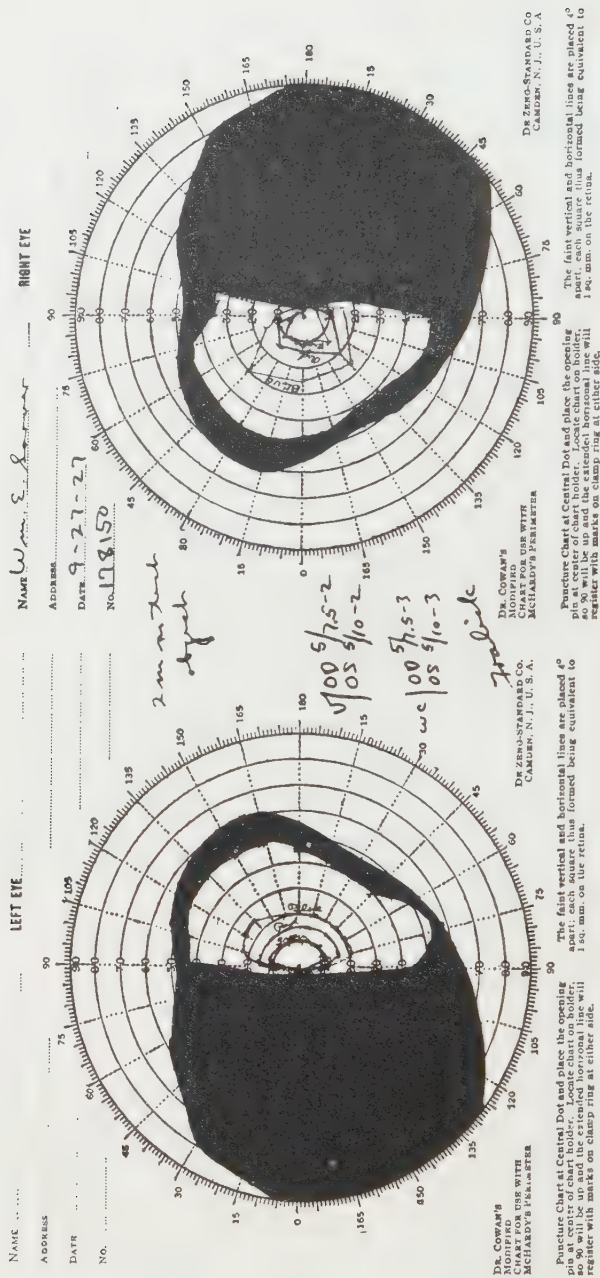


FIG. 156. Bitemporal hemianopsia from a pituitary adenoma which appeared in front of the chiasm, pushing the optic nerves upward and outward. The visual fields returned practically to normal after operation, showing that the tension on the crossed fibers in the chiasm had produced only a physiological block.

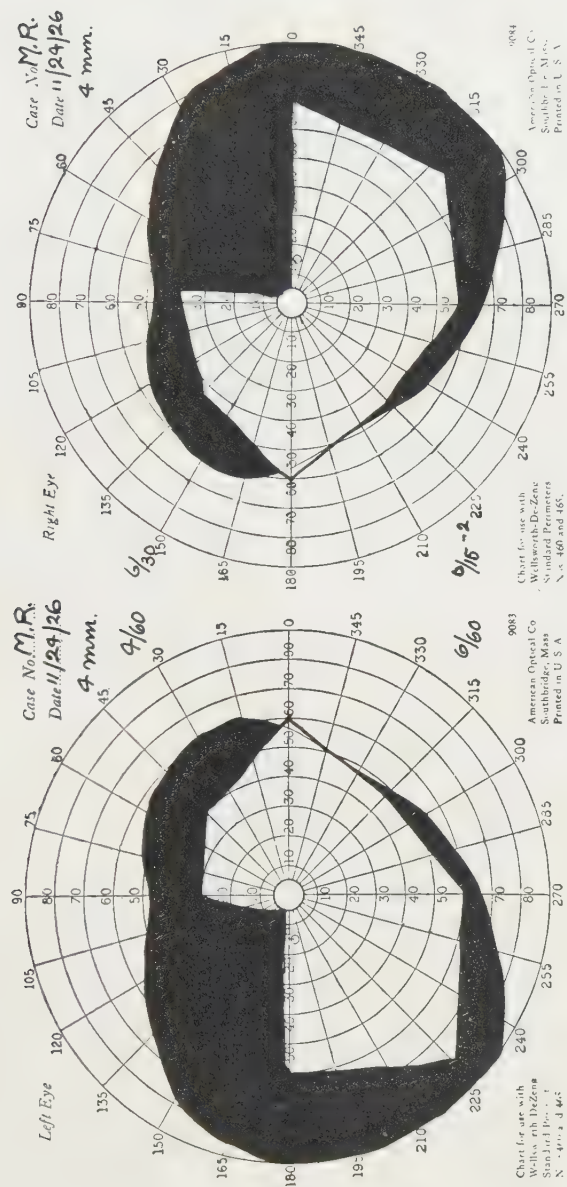


FIG. 157. Practically symmetrical upper quadrant defects due to an hypophyseal adenoma pressing the chiasm upward and backward and elevating and separating the optic nerves. The optic discs showed a primary atrophy, but the defects were due to a physiological block, since the fields returned promptly to normal after operation.

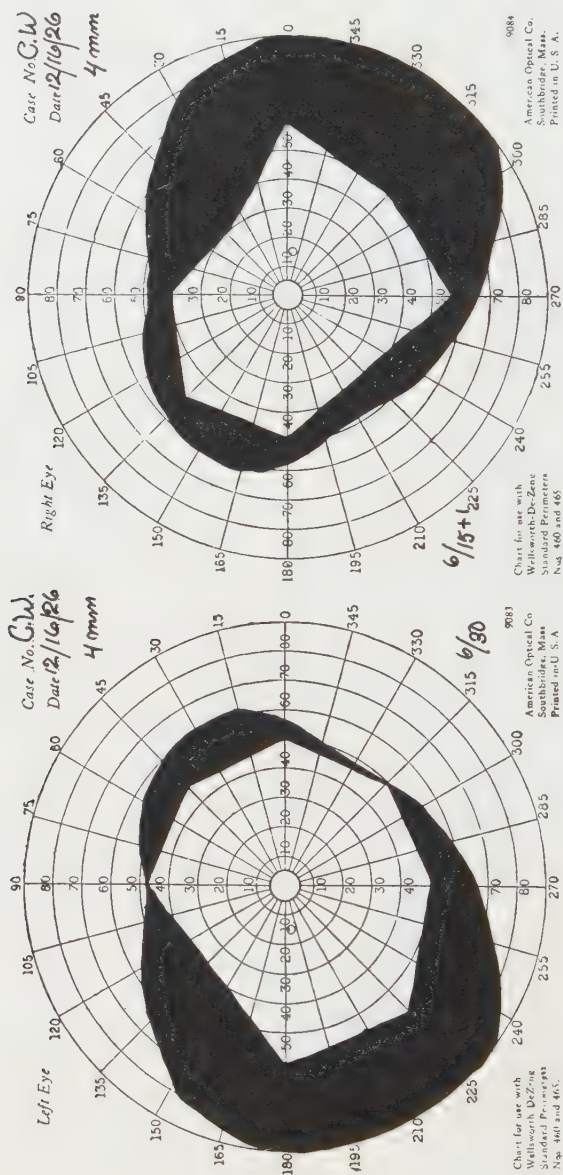


FIG. 158. Bitemporal slant in an early case of pituitary adenoma. The patient had not noted any visual loss, her only complaint being pain.

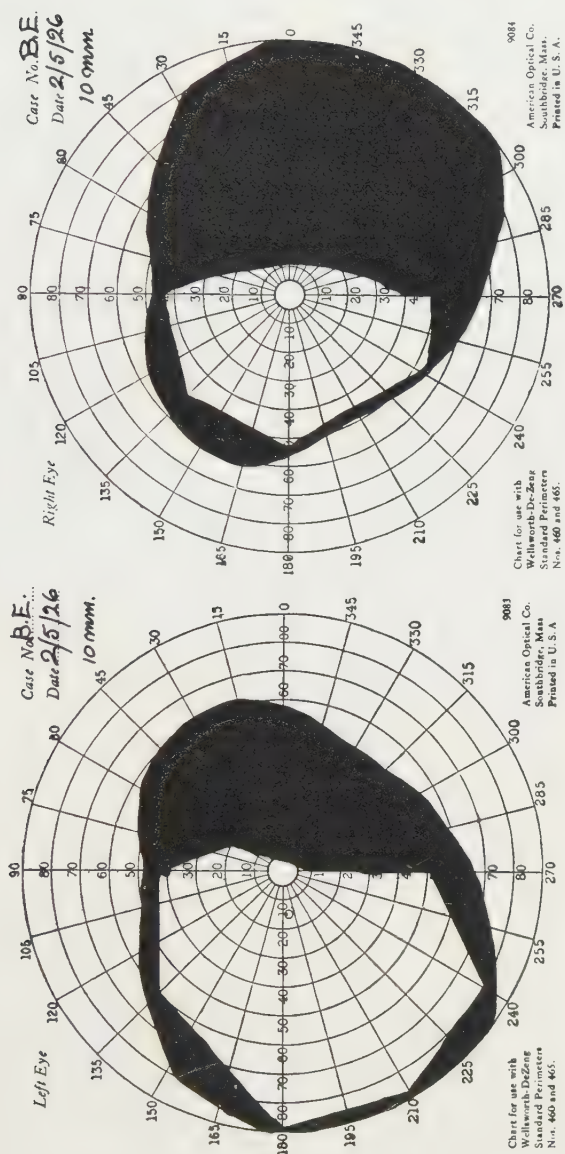


FIG. 159. Right homonymous hemianopsia produced by a large hypophyseal adenoma.

left than directly upward. For this reason a complete temporal hemianopsia on one side and a temporal upper quadrant defect on the other is a common finding. Further extension of the growth may result in complete blindness in one eye and a temporal hemianopsia in the other.

While bitemporal field defects have usually been considered the characteristic picture in pituitary tumors, we have frequently found a homonymous hemianopsia, *i.e.*, temporal blindness on one side, nasal blindness on the other (fig. 159). Walker and Cushing (3) found homonymous hemianopsia in 14.8 per cent of their pituitary cases. This departure from the classical picture is usually the result of pressure on one side of the chiasm from an irregular upward extension of the intrasellar tumor. Much more rarely the tumor has produced the same picture by pressure on one of the optic tracts posterior to the chiasm. The great majority of hypophyseal tumors, however, extend upward beneath and in front of the optic chiasm, displacing the optic nerves laterally and at times stretching them into thin ribbons. It is only in the exceptional case, in which the chiasm is placed far forward, the optic nerves being correspondingly shortened, that pressure on an optic tract occurs before trauma to the chiasm.

Bitemporal or homonymous hemianopsia, the former the more common, also results from downward pressure on the optic nerves by tumors originating above them. The usual tumors in this situation, Rathke's pouch or craniopharyngeal duct cysts and adamantinomata are related embryologically to the pituitary, but due to the latter's rotation during development, are carried upward along the infundibulum. The first visual loss associated with these suprachiasmal lesions is a lower quadrant defect, in contrast to the upper defects from primary intrasellar tumors. Depending on the exact direction of the downward pressure, either a bitemporal, or right or left homonymous lower quadrant visual field defect will result.

Similar lower quadrant defects may occur in connection with subchiasmal tumors or those primarily intrasellar, confusing the diagnosis. This simulation of symptoms between tumors above and below the optic nerves and chiasm is due to upward pressure of the nerves or chiasm against the comparatively unyielding adjacent structures. These are the internal carotid, the anterior cerebral and the anterior communicating arteries, the optic foramina, and the dural band connecting the anterior clinoid processes. Such firm and compari-

tively narrow structures may, in the presence of a large hypophyseal tumor, cut a groove of varying depth on the superior or lateral surfaces of the optic nerves, chiasm, or both (fig. 160). Similar findings have been reported by Turck, Sachs, Erdheim, Bartels, De Schweinitz and Holloway, Hirsch, Cushing and Walker, and have been recently summarized by Fay and Grant (5). The differential diagnosis will depend on the presence of other localizing symptoms, particularly changes in the sella, and the presence of a primary optic atrophy,



FIG. 160. Anterior communicating artery cutting a groove in both optic tracts, but principally in the left, with a resulting right homonymous hemianopsia. The large, irregular adenoma had pushed the internal carotids widely apart. The tumor appeared in front and behind the chiasm, on the outer side of both optic nerves and tracts and extended laterally beyond the vessels. The drawing was made at autopsy following death from pneumonia.

rather than choked disc as might be expected in a supra-chiasmal lesion. The latter does occur, however, in some pituitary tumors, due to the backward or more rarely the extreme upward extension of the tumor. Bitemporal hemianopsia is also produced by meningiomas (endotheliomas) of the suprasellar and cribriform plate regions. An endothelioma originating in the optic nerve sheath may cause total blindness in one eye and a temporal hemianopsia in the other. Primary gliomas of the chiasm and optic nerves sometimes produce a



FIG. 161. Ventriculogram showing unilateral hydrocephalus due to obstruction of the right foramen of Monro by a suprasellar craniopharyngeal duct cyst. The right ventricle is greatly enlarged and extends across the midline, indenting the left anterior horn.

somewhat similar picture, but as pointed out by Cushing (6), the hemianopsia is not so sharply drawn as in the case of pituitary tumors. The loss of vision in these gliomas is so very rapid as to be of definite diagnostic significance.

The differential diagnosis between hypophyseal lesions, neighborhood meningiomas, and primary tumors of the optic nerves rests largely on the x-ray evidence of local pressure changes. The cribiform plate endotheliomas do not, as a rule, cause sellar distortion. A bitemporal hemianopsia in the presence of a relatively normal sella turcica is, therefore, presumptive evidence of an endothelioma. Unilateral or bilateral anosmia will practically confirm the latter diagnosis.

The fundus examination is quite indicative of local pressure changes. With few exceptions, tumors of the pituitary and hypophyseal region produce a primary optic atrophy by direct pressure on the nerves and chiasm. The optic disc is pale and in advanced cases greyish white. A similar atrophy is noted in primary tumors of the optic nerves. In the latter, according to Cushing (6), the tumor may extend through the nerve to the disc, giving the appearance of papilloedema.

Occasionally in very large pituitary tumors and much more commonly in the suprachiasmal lesions, such as craniopharyngeal duct cysts, a choking of the optic discs will be found. This is due in most cases to encroachment on the third ventricle with obstruction of one or both foramina of Monro (fig. 161). Rarely the tumor extends backward sufficiently to displace the pons and thereby interfere with the flow of cerebrospinal fluid through the aqueduct of Sylvius. Such a large tumor may also fill the interpeduncular space, partially obstructing the main cerebrospinal pathway to the cortex, with resulting hydrocephalus.

Papilloedema in pituitary tumor cases may also be due to a coincident, but unrelated tumor in some other portion of the brain, the hypophyseal growth being only incidental. Such a combination of tumors was observed recently in our clinic. The patient was a far advanced acromegalic with enormous tongue, hands and feet. He complained of almost constant excruciating, generalized headaches, associated with frequent projectile vomiting. The visual fields showed large central scotomata and a general contraction for form and color. No suggestion of a quadrant defect was present. The

fundus examination showed choked discs of six diopters, but no evidence of primary optic atrophy. A diagnosis of two intracranial lesions was made and at operation an enormous solid glioma of the right posterior parietal lobe was found. A moderately large adenoma of the pituitary was seen, but neither the optic nerves nor chiasm were pressed upon by the intrasellar growth.

Further evidence of local pressure is occasionally demonstrated by certain cranial nerve palsies. The third, fourth, and sixth nerves lie on either side of the sella turcica and it is somewhat surprising that they are so seldom involved. In those patients showing partial or complete paralysis of these cranial nerves, we have found at operation a marked lateral projection of the hypophyseal tumor, the process extending under the optic nerve and carotid artery to the sphenoidal fissure.

The headache associated with pituitary tumors has been often described as bitemporal, but many of our patients have complained of pain only on one side. At times the pain is frontal. Some do not localize it, but others complain of a severe, dull (in contradistinction to sharp) headache, deep within the head. Many patients use the terms "pressure" or "bursting" in describing their pain. It is generally supposed to be due to capsular distention. Certainly this type of pain often disappears coincidentally with the destruction of the diaphragm of the sella, if we may assume that the onset of visual changes is an indication of such perforation.

The headaches later in the disease are usually more diffuse, and although often most severe in the frontal region, resemble those due to cerebral tumors in general rather than the more localized pressure pain of the purely intrasellar growth. The patient often volunteers the statement that "since the visual disturbances the headaches seem to be entirely different." An explanation for these secondary headaches has not, so far as we know, been given. I believe we now have a satisfactory solution. At operation, in patients suffering from the secondary type of pituitary headache, we have noted almost complete absence of cerebrospinal fluid in the subarachnoid space over the frontal and the anterior portion of the parietal lobes. A slight degree of hydrocephalus has usually been present as evidenced by the depth at which the lateral ventricle was punctured. In most cases the hypophyseal tumor had encroached upon or completely obliterated the cisterna chiasmatis without, however, pressing upon the floor of the

third ventricle. There was no suggestion that either foramen of Monro was, even to a slight extent, obstructed. On removing the pituitary tumor, thereby exposing the cisterna interpeduncularis, there was invariably a gush of cerebrospinal fluid under increased pressure.

Autopsies on unoperated cases have shown a similar picture. In each case there has been obliteration of the anterior cisterna in the pituitary region with a distention of the cisterna immediately pos-

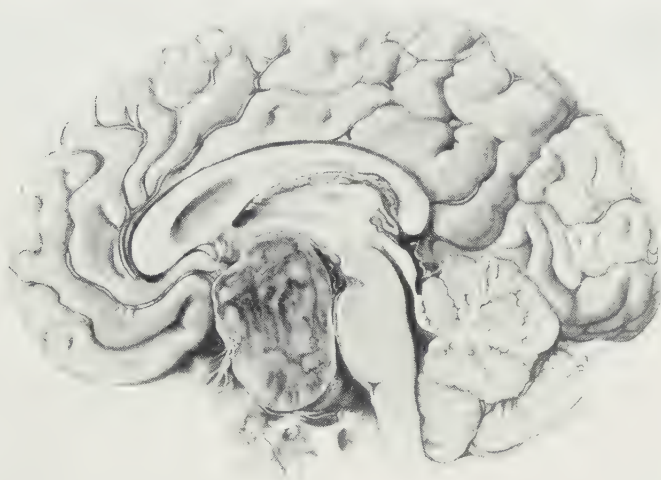


FIG. 162. Large adenoma of the pituitary extending into the third ventricle, but not causing a marked hydrocephalus since the foramina of Monro are not obstructed.

terior to the tumor, and in such cases a moderate hydrocephalus was found, although the third ventricle and foramina of Monro were intact. A pituitary tumor may encroach considerably on the third ventricle without obstructing the foramina of Monro since the latter are situated well up on its lateral walls (fig. 162).

We believe the secondary headaches caused by hypophyseal tumors are the result of a partial obstruction to the circulation of the cerebrospinal fluid. The obliteration of the cisterna chiasmatis blocks some of the most important pathways by which the cerebrospinal

fluid reaches the great absorptive areas over the cerebral hemispheres. The comparatively dry subarachnoid space observed in the frontal and anterior parietal regions, the evident distention of the cysterna posterior to the chiasm, and the moderate hydrocephalus all point to such a conclusion. Fortunately, the blocking is not sufficiently extensive, except in a few isolated cases, to produce choking of the optic discs.

The manifestations of generalized pressure, observed rather commonly in suprachiasmal lesions and occasionally in tumors originating within the sella, are identical with those produced by other intracranial tumors. As noted before these signs and symptoms of increased intracranial pressure are generally due to interference with the flow of cerebrospinal fluid. Headaches, nausea and vomiting are the principal symptoms, but the latter usually occur in pituitary cases only when marked hydrocephalus has developed. The principal x-ray indication of generalized pressure is the evidence of convolutional atrophy, often spoken of as digital markings, seen most prominently in the frontal and parietal regions. In young subjects separation of the suture lines is an important finding. The coronal suture usually shows the greatest separation.

The fundus examination shows varying degrees of papilloedema and in advanced cases some secondary atrophy may be present. Occasionally a primary optic atrophy will have a papilloedema superimposed upon it. The visual fields, unless hemianopsias were previously present, show simply a concentric contraction, often with a large central scotoma.

SUMMARY

Tumors and other expanding lesions of the hypophysis and pituitary region manifest either local or general intracranial pressure phenomena. The local pressure changes produced by intrasellar tumors are characterized by enlargement of the sella turcica, thinning and finally erosion of its floor, and by partial or complete destruction of the posterior and to a relatively less extent of the anterior clinoid processes.

Tumors on either side, or above, or behind the sella turcica, and subtentorial lesions associated with hydrocephalus, may cause changes in the sella, or in the posterior clinoid process alone, which simulate the so-called characteristic changes produced by intrasellar tumors.

Encroachment on the general intracranial space by upward growth

of the hypophyseal tumor results first in visual field defects. later, if the circulation of the cerebrospinal fluid is obstructed, general pressure phenomena appear. Early perimetric examinations may show a temporal slant, soon to be enlarged to quadrant defects, later to bitemporal, or less commonly to a homonymous hemianopsia, and finally to complete loss of vision in one eye, temporal or nasal hemianopsia in the other. Upper quadrant defects are usually associated with intrasellar tumors; lower quadrant defects with suprachiasmal lesions. Lower quadrant visual field defects may, however, occur with tumors primarily intrasellar, the destructive lesion being produced by pressure of the optic nerves, or chiasm against the superimposed internal carotid, anterior cerebral, or anterior communicating arteries, the optic foramina or a dural band connecting the anterior clinoid processes. Neighboring tumors and those of the optic nerve or its sheath may produce visual field defects suggesting pressure on the optic nerves by a pituitary lesion. Ocular fundus examinations show a primary optic atrophy unless general intracranial pressure is present, then papilloedema will be noted.

The evidences of generalized intracranial pressure are headaches, associated in advanced cases with nausea and vomiting, dimness of vision due to papilloedema, and x-ray changes in the skull. The latter are convolutional atrophies of the inner table, appearing as digital makings, and in children separation of the cranial sutures.

Early pituitary headaches are probably due to intracapsular pressure. Those occurring latter, after marked visual changes occur, are in our opinion due to a moderate general increase in intracranial pressure, secondary to partial or complete obliteration of the cisterna chiasmatis with a resulting block to the circulation of cerebrospinal fluid over the frontal and parietal regions.

DISCUSSION

The following questions submitted to Dr. Peet before the Commission, together with the answers to them, are here reported verbatim.

DR. GLOBUS: I would like to ask Dr. Peet whether in trying to give an explanation for the dry brain in this group of pituitary neoplasm he has not used an explanation given by Dr. Dandy in the so-called communicating internal hydrocephalus.

DR. PEET: If I remember the communication of Dr. Dandy to which Dr. Globus refers, the cases reported were those in which the arachnoid had become

more or less adherent to the pia from some previous inflammatory condition. I doubt if this is the explanation in these pituitary cases since the fluid could circulate if the anterior cisterna was not obstructed. The mechanical block, although of different etiology in the cases described by Dandy and those considered here, acts in a similar way. In addition to the inflammatory types I think there are certain cases in which the arachnoid was never separated with consequent absence of a normal subarachnoid space. Some of our cases of hydrocephalus are in children in whom the communicating channels apparently never developed.

DR. TIMME: I would like to ask Dr. Peet just three questions. First, what is the relative proportion of the homonymous hemianopsia and the bitemporal hemianopsia.

DR. PEET: Twenty-three per cent of our pituitary cases had homonymous hemianopsia, 40 per cent had bitemporal hemianopsia, and about 4 per cent had blindness in one eye and either nasal or temporal hemianopsia in the other. Bitemporal hemianopsia was only twice as frequent as homonymous hemianopsia.

DR. TIMME: What are the earliest symptoms that would lead you definitely to operate for pituitary lesions?

DR. PEET: Diminution of vision.

DR. TIMME: Until you had that you would not advise operation?

DR. PEET: We have operated because of excruciating headache or very severe sharp intracranial pain when the visual disturbance was slight, but this is exceptional.

DR. TIMME: Together with x-ray findings?

DR. PEET: Yes.

DR. TIMME: May I ask what your mortality rate is in pituitary neoplasms, operated upon?

DR. PEET: We have about 21 per cent mortality from all causes, chiefly pneumonia. A great many of our patients are very far advanced, having frequent spells of coma. As an example one patient had on three occasions at our hospital, and on several occasions before admission, gone into deep coma from which he could not be aroused for several days. A few days after operation, the patient again went into a coma and did not come out of it again. Whether you can honestly claim this as an operative mortality is questionable. On the other hand, I have had quite a number die in the same way before I was prepared to operate.

The illustration of the pituitary tumor shown in the cross-section of the brain was made from another case which quietly passed out without operation. So taking our patients actually operated upon, in comparison to those unoperated

upon which also have had a mortality of about 20 per cent, I do not believe the operative mortality can be entirely blamed on the operation.

I believe the only indication for surgery in pituitary lesions is definite evidence of pressure, either a visual field change, which you have every reason to expect will progress to blindness or incapacitating headaches or pain.

I did not mention our explanation (I hesitate considerably to do so) for the pain of trigeminal type which a few pituitary patients have had. Probably some of you have noted in operating with local anaesthesia on pituitary cases that the only portion of the dura which is sensitive to touch is that covering the anterior clinoid processes.

In the two patients this year who had severe pain of trigeminal type the pituitary tumor had grown up and over an anterior clinoid process. Whether pressure on this sensitive dura was the cause of their pain, has not been proven, but removal of the tumor gave relief.

I would like to ask Dr. Frazier if his patients who showed a good deal of sub-arachnoid fluid were not patients that were comparatively free from headache, or those in whom at least the headache had not been a striking manifestation. Our cases with the dry brain were the patients who had severe incapacitating headaches. We have found plenty of fluid in patients on whom we operated for visual disturbances unassociated with headache. I do not believe that pressure upon the optic tracts in itself would give headache. I have deliberately pressed upon the optic nerve while operating under local anesthesia to see if I could get any manifestations, visual or otherwise, but in no instance has the patient had either pain or visual phenomena.

DR. FRAZIER: I think I can answer Dr. Peet's question by saying we have estimated that in only 5 per cent of our entire series was the headache so serious a factor as to make one feel justified in doing something for its relief by surgical means.

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CHAPTER XXVII
THE DANGERS OF DIAGNOSTIC LUMBAR PUNCTURE IN
INCREASED INTRACRANIAL PRESSURE DUE TO
BRAIN TUMOR¹

WITH A REVIEW OF TWO HUNDRED CASES IN WHICH
LUMBAR PUNCTURE WAS DONE

CLEMENT B. MASSON, M.D.

THE belief is widespread among neurological surgeons and others that lumbar puncture in patients with increased intracranial pressure due to brain tumor is a dangerous and an unwarranted procedure. At the New York Neurological Institute, we have never hesitated— unless the signs and symptoms pointed to a subtentorial new growth—to perform lumbar puncture for diagnostic purposes. It seemed, therefore, that it would be of interest to review two hundred of our cases in which this procedure was done.

The literature on the subject of the danger of lumbar puncture in states of increased intracranial pressure is not large, and the writer has been able to find few studies of a large series of cases. In most instances only isolated reports of single cases in which untoward symptoms and even death has occurred after this procedure, have been published. Numerous writers speak of the dangers of lumbar puncture in brain tumors without going into any details on the subject.

Cushing (1), in a paper on, "Some aspects of the pathological physiology of intracranial tumors," makes the following statement:

In all cases in which pressure phenomena are present and the obstructed fluid has acquired an increased degree of tension, it collects and distends the basilar cisternae, finding its way into the optic sheaths; hence the choked disc. It also passes into the olfactory nerves; hence its occasional escape from the nares (rhinorrhea); and into the spinal canal, where it may be demonstrated under increased tension if one wishes to take the risk of performing a lumbar puncture in those cases. . . . In conclusion, one recognized characteristic of the brain under pressure is its tendency to herniate through a cranial defect, and as there is nor-

¹ From the Neuro-surgical Clinic (Dr. Elsberg) and the Neurological Divisions of the New York Neurological Institute.

mally an opening at the foramen magnum, a certain degree of protrusion is usually present there. In the presence of such conditions the withdrawal of the cerebrospinal fluid from the spinal meninges by a lumbar puncture is often hazardous, as it may tend to a sudden wedging of the bulb in the opening, with anemia and paralysis of the vital centers.

Comfort (2), in a series of 73 cases of brain tumor, 35 of which were proved at operation or autopsy, and in all of which lumbar puncture had been performed, mentions no instance of dangerous symptoms or death following such procedure.

Connor (3) states that, "in a few cases of uremia and brain tumor death has followed within a few hours, the withdrawal of a large amount of fluid. . . . Those conditions in which the greatly increased cerebrospinal fluid pressure has existed for some time, *e.g.*, brain tumors—are the ones apparently which bear least well the sudden removal of a large quantity of fluid." This is a warning against a medical *decompression*, but should not be interpreted as *prima facie* evidence against a *diagnostic* puncture even in a case of brain tumor in whom long continued increased intracranial pressure has existed.

Frazier (4) speaks of the use of lumbar puncture during cranial operations, to relieve intracranial pressure. In one case 50 cc. of spinal fluid were removed so as to enable the operator to open the dura.

The material on which this report is based is shown in table XXVII. These 200 cases are not a selected group. Two hundred consecutive patients with increased intracranial pressure due to proved or presumed brain tumor, in whom lumbar puncture was performed were used as the basis for the study. In the majority of the cases of tumor verified by operation or autopsy the growth was a glioma of one or another type, although neurinomas, meningeal fibroblastomas (meningiomas, endotheliomas) and other types of intracranial neoplasm are represented in the series. The growths were located in various parts of the brain, and cases of subtentorial tumor were included although the question of the danger of lumbar puncture in tumors in the posterior cranial fossa is quite another matter, and lumbar puncture in subtentorial expanding lesions excepting after operations in which a suboccipital craniotomy with removal of the margin of the foramen magnum and wide incision of the dura has been performed is probably always contraindicated.

In what follows, the effort has been made to correlate the nature of the neoplasm, its location and size, the x-ray evidence of increased

intracranial pressure, the degree of papilledema if present, the intraventricular pressure of the cerebrospinal fluid (when measured), the amount of tension of the dura in the patients subjected to operation, the spinal manometric pressure (when measured), and, finally, the amount of fluid removed by lumbar puncture whenever this was definitely recorded, so as to arrive at a conclusion regarding the actual danger, if such there be, of lumbar puncture in states of increased intracranial pressure due to suspected tumor of the brain.

In the majority of the 200 cases not more than 5 cc. of cerebrospinal fluid for examination were withdrawn by puncture of the spine and when the fluid was found to escape under marked increase of pressure the stylet was reintroduced into the needle and the fluid was allowed

TABLE XXVII
FINDINGS IN 200 CASES OF LUMBAR PUNCTURE

	NUMBER OF CASES	VERIFIED	NOT VERIFIED
Total number of cases.....	200	94	106
Supratentorial newgrowths	141		
No papilloedema in.....	39	19	20
Papilloedema in.....	102	43	59
Infratentorial new growths	59		
No papilloedema in.....	17	8	9
Papilloedema in.....	42	24	18

to drop out slowly. The needles used for the puncture were of fine calibre and of the Quincke type. It is hardly necessary to mention that needles of coarse calibre should never be used. A needle of large calibre might allow fluid under greatly increased pressure to escape so very quickly that a very sudden marked change in intracranial pressure conditions might be brought about which might cause serious symptoms and even a fatality from the sudden diminution of pressure within the skull. Lumbar puncture as carried out in the cases reviewed has been limited to that of a diagnostic procedure done with the patient lying in the right or left lateral prone position, and kept in the supine position for at least twenty-four hours thereafter. In some instances, however, confused patients have, despite great care, gotten out of bed soon after the puncture but with no untoward results.

TABLE XXVIII
LUMBAR PUNCTURE IN VERIFIED TUMORS

A. Infratentorial expanding lesions: 32 verified by operation or autopsy

The puncture was performed before the diagnosis of a growth in the posterior fossa had been made and proved by operation or autopsy.

	NUMBER OF CASES	TIMES LUMBAR PUNCTURE WAS PER- FORMED	RESULTS
(a) Without papilloedema: 8			
No evidence of pressure: X-ray negative; spinal fluid not under pres- sure	4	4	3 cases no effect; 1 case headache not severe
Evidence of pressure: Convolutional atrophy, headache, drowsiness	4	4	3 cases no change; 1 case head- ache not severe
(b) With papilloedema: 24 (+2 dipters to +7 dipters)			
No evidence of pressure: At operation tension of dura not increased	1	1	Slight nausea day before punc- ture and condition aggravated for two days thereafter
Evidence of pressure: Mucoid cyst of the arach- noid above foramen magnum, lying upon medulla	1	5	3 times slight headache; 2 times none
Left cerebellar abscess with 60 cc. of pus	1	1	12 cc. of fluid removed with no new symptoms, no headache
Meningeal fibroblastoma in lateral recess	1	1	Punctured with patient in sitting posture; 5 cc. removed; for a few minutes patient became pale, perspired freely, pulse rapid, did not faint. Spinal fluid yellow
Endotheliomas, gliomas, nervus acusticus tu- mors, etc.	20	22	18 no effect; 3 cases headache for a day or two; 1 case severe headache. In two of the cases two punctures were performed before operation without any ensuing symptoms

TABLE XXVIII—Continued

B. Supratentorial tumors: 62 cases verified by operation or autopsy

	NUMBER OF CASES	TIMES LUMBAR PUNCTURE WAS PER- FORMED	RESULTS
(a) Without papilloedema: 19			
Pituitary tumors:			
No evidence of increased intracranial pressure	2	2	No effect in 1; slight headache in 1
Endotheliomas:			
With other signs of increased intracranial pressure	3	3	No effect in 2; headache, nausea and vomiting for three days in 1
Gliomas:			
Spinal fluid pressure 70 mm. water	1	1	No change
Spinal fluid pressure 360 mm. water	1	1	Headache increased for forty-eight hours
Tense dura found at operation	6	7	No change in 6; headache for four days in 1
Fibro sarcomas, gummas, etc.	6	6	No change
(b) With papilloedema: 43			
Gliomas:			
Suprasellar tumors (papilloedema, +4 D)	2	2	No change in 1, headache increased in 1
Endotheliomas (papilloedema, +6 D)	11	11	No change in 8; headache for twenty-four to forty-eight hours in 3
Cholesteatoma (papilloedema, +5 D)	1	2	Punctures performed two years apart, no effect from either puncture
Gliomas (spongioblastoma, astrocytoma and other ripe and unripe forms)			
Papilledema low grade up to +1 D	6	7	No change; in 1 case spinal pressure was 500 mm.; in a second case punctured twice before operation; pressure over 580 mm.; no effect noted
Papilloedema, 2 to +7 D	20	20	No change in 19; severe headache for several days in 1; spinal fluid pressure not increased in 1; in 19 pressure was above normal; in two patients as high as 520 mm.
Sarcomas, etc. (+3 to +5 D)	3	3	No change in 1; headache worse for two days in 1; headache relieved in 1

Table XXVIII, *A*, shows that not even in subtentorial expanding lesions were any serious untoward effects produced by lumbar puncture and the removal of a small amount of cerebrospinal fluid. If at the time the diagnosis of a subtentorial expanding lesion had been made or suspected, a lumbar puncture would not and should not have been performed.

This group of cases is of great interest, as it shows that even in tumors in the posterior cranial fossa, the danger of lumbar puncture is not very great. Notwithstanding the results in this series, a sufficient number of cases have been recorded in the literature in which serious symptoms and death followed the withdrawal of fluid by puncture of the spinal subarachnoid space that this procedure should not be carried out if a subtentorial expanding lesion is diagnosed or suspected.

In this group (table XXVIII, *B*), there is one additional case that deserves more extended notice. A patient, M. C., had been operated upon, an irremovable spongioblastoma multiforme had been exposed in the left temporal and parietal lobes, only a specimen removed for verification, and a large defect in the bone left for decompressive purposes. The patient was readmitted into the hospital several times and some relief obtained by the removal of fluid by lumbar puncture. The patient was admitted again and upon lumbar puncture and withdrawal of a considerable amount of fluid, the bulging cerebral hernia suddenly flattened, the pulse and respiration became shallow, and the patient remained in a condition of collapse for ten minutes, after which she recovered.

This was the most serious effect from lumbar puncture that we have seen in the entire series of supratentorial expanding lesions here recorded. In this case it must be remembered, however, that the lumbar puncture was not performed for diagnosis, but for its decompressive effect and the temporary serious symptoms were the result of therapeutic and not of a diagnostic procedure.

From this summary, it will be seen that in 94 patients with verified supratentorial and infratentorial expanding lesions within the cranial cavity, no serious untoward results followed lumbar puncture and the removal of a small amount of cerebrospinal fluid. There was no fatality in a single patient and with the one exception above noted, the only result of the puncture was an increase of headache in 19 patients, in most of them only slight, nausea in 2 patients and faintness in one.

TABLE XXIX

LUMBAR PUNCTURE IN TUMORS AND EXPANDING LESIONS NOT VERIFIED BY
OPERATION OR AUTOPSY*A. Possible infratentorial expanding lesions*

	NUMBER OF CASES	TIMES LUMBAR PUNCTURE WAS PER- FORMED	RESULTS
(a) Without papilloedema: 10			
No evidence of pressure:			
Fourth ventricle tumor?	1	1	No change
Cerebellar, pontine and nervus acusticus?	4	4	No change
Posterior fossa suspect	1	1	Headache increased vomiting for twenty-four hours
Cerebellar with marked hydrocephalus	1	1	Marked increase in headache after lumbar puncture
Evidence of pressure:			
Cerebellar and brain stem; spinal fluid under pressure	1	1	Headache made worse
Questionable glioma or tuberculoma; spinal fluid pressure 240 mm. (water)	1	1	No change following lumbar puncture
(b) With papilloedema: 18			
Very slight blurring of discs			
Evidence of pressure:			
Tuberculoma? fluid under pressure	1	1	No change
Angle tumor?	1	1	No change
Cerebellar?	1	1	No change
Papilloedema +2 Diopters to +6 Diopters			
Cerebellar	1	1	Vomited and had pain in back of neck and head
Posterior fossa	1	2	No change; once in sitting posture; once lying down
Posterior fossa	7	7	No change
Spinal fluid under con- siderable pressure	1	1	No change
Posterior fossa	1	1	Headache, nausea and vomiting
Posterior fossa	1	1	Slight headache

TABLE XXIX—Continued

	NUMBER OF CASES	TIMES LUMBAR PUNCTURE WAS PER- FORMED	RESULTS
Posterior fossa	1	1	Increased headache present at the time
Posterior fossa	1	1	Severe headache for forty-eight hours
Cerebellar and mid brain tuberculoma?	1	3	No effect: pressure 380 mm.

B. Suspected supratentorial expanding lesions: 78

(a) Without papilloedema: 20

Evidence of pressure:			
Dura tense, ventricular system collapsed	1	1	No change
Spinal fluid under increased pressure	2	2	No change
Right frontal	1	1	No change
Right temporal lobe abscess; spinal fluid pressure increased	1	2	No change
Pituitary?	1	1	Headache for several days thereafter
No evidence of pressure:			
Localization?	5	5	No change
Frontal lobe?	1	1	Headache for three days
Frontal lobe?	1	1	Confused as usual after lumbar puncture
Parietal lobe?	1	1	No change
Frontal and parietal lobes?	1	1	Jacksonian attack in right side of body continued
Tuberculoma?	1	1	No change
Pituitary?	2	2	1 no change; 1 typical post-lumbar puncture headache
Localization?	1	1	Slight headache for one day
Frontal lobe	1	1	No change

(b) With papilloedema: 48

Papilloedema from +1 diopter to +7 diopters

Evidence of pressure:			
Beginning papilloedema	2	2	No change
Right temporo-sphenoidal lobe	3	4	No change in 2 cases; 1 case had 2 punctures; no change

TABLE XXIX—*Continued*

	NUMBER OF CASES	TIMES LUMBAR PUNCTURE WAS PER- FORMED	RESULTS
Right frontal lobe	3	3	No change
Right frontal lobe, right posterior horn pressure 580 mm. (water)	1	1	Lumbar puncture done in Trendelenberg position; severe headache for one day
Right frontal lobe, dura white and tense at operation	1	1	Felt better after lumbar puncture
Right frontal lobe; spinal fluid 380 mm. pressure	1	1	Headache and vomiting for two days
Left frontal lobe	5	5	No change
Left frontal lobe	1	1	Headache for three days
Left frontal lobe, +6 diopters	1	2	1 puncture no effect; 1 severe headache
Bilateral frontal tumor? +5 diopters	1	1	No change
Left hemisphere of brain involved	2	2	No change
Left hemisphere of brain involved, with increased density back of left orbit, lumbar puncture showed increased pressure	1	1	No change
Left hemisphere, deep seated lesion. Marked increased tension of dura	1	1	No change
Right frontal and parietal lobes involved, marked increase in tension of dura	2	2	No change
Right frontal and parietal lobes exceedingly tense dura lumbar puncture pressure 280 mm.	1	1	No change
Left parietal lobe; pressure 220 mm.	1	1	Punctured in sitting position; no change
Right frontal and parietal lobes; +2 diopters	1	4	20 cc. of fluid removed each time with improvement
Right frontal and parietal lobes	1	1	Vomiting, headache and irrational actions as before lumbar puncture

TABLE XXIX—*Continued*

	NUMBER OF CASES	TIMES LUMBAR PUNCTURE WAS PER- FORMED	RESULTS
Right frontal and parietal lobes	1	1	No change
Right parietal and temporal lobes involved	1	1	No change
Left parietal lobe, deep infiltrating tumor? at operation dura found very tense	1	1	Headache the same as before lumbar puncture
Pituitary? (blind)	1	1	No change
<i>Brain tumor? unlocalized</i>	5	5	No change
Skull bones atrophied	1	1	No change
Sella almost completely destroyed	1	1	No change
Lumbar puncture pressure 420 mm.; right and left posterior horns small amount of fluid	1	1	No change
Nothing of note excepting the papilloedema	1	1	Headache for three days
Brain moderately tense +5 diopters	1	1	No change
Lumbar puncture showed "tremendous pressure"	1	1	No effect
Spinal fluid under 160 mm. pressure	1	1	No effect
Patient aged two and one-half years, marked signs of pressure	1	1	No effect
+4 diopters, convolitional atrophy	1	1	No effect
Patient almost blind	1	1	No change

With papilloedema (but without other signs of pressure): 10

Evidence of pressure:			
Pituitary	1	1	No change
Right parietal lobe, +5 diopters; no signs of increased intracranial pressure at operation	1	1	No change
Left parietal lobe, early papilloedema	3	3	No change
Frontal lobe (abscess)	1	4	No change

TABLE XXIX—*Concluded*

	NUMBER OF CASES	TIMES LUMBAR PUNCTURE WAS PER- FORMED	RESULTS
Right frontal lobe, spinal fluid not under tension; dura not under tension; discs +6 diopters	1	1	No change in blood pressure, pulse or respirations
Right frontal lobe, +4 diopters	1	1	Severe headache and nausea for three days
Right frontal, no signs of pressure at operation, +3 diopters	1	1	No change
Third ventricle tumor	1	1	No change

In the exception, the puncture and withdrawal of fluid was not done for diagnostic purposes, but as a therapeutic measure and therefore does not properly belong in this discussion.

In addition to these 78 cases of suspected supratentorial tumors not verified, there was 1 case that should receive special mention.

(N. I. N. Y. A11686 H.) G. M. Aged twenty-two years, admitted August 26, 1926, complaining of weakness of left side of the body, headache and blurred vision. Her illness began March 4, 1925, with a sudden feeling of impending calamity and was progressive in its course. While playing cards she suddenly felt greatly depressed for several minutes. The next morning she had a similar attack and since that time she has had two to three attacks a week.

On April 15, 1925, the patient's mother found her in bed unconscious having convulsive movements. She has had seven such attacks since that date which often occurred with her menstrual periods. In September, 1925, after swimming she had sudden severe headache, could not walk, and had to be carried into a house at which time it was found that both sides of her body were weak. The power on the right side soon returned but the left side remained weak. In August, 1926, she had another attack followed by weakness of the left face, arm and leg, and since that time she has had a good deal of headache with attacks of projectile vomiting. The left sided weakness has grown more marked, and recently she has complained of photophobia and poor vision.

Neurological examination: Although the patient had been in bed for three weeks previous to admission to the hospital she was able to walk to her room with assistance. She is able to stand on either foot alone, but can use the right foot and leg better than the left. There is marked weakness of the left hand grip and diminished power of extension and flexion of the left foot. Finger to nose test is done normally on the right but there is slight wavering on the left.

Finger to thumb is slowly performed on the left, but normal on the right; heel to knee test: normal on the right, much more slowly carried out on the left. No distinct ataxia; some diminution of the check element in the left arm; some adiadokokinesis on the left. Speech normal. The deep reflexes are slightly more active on the left side of the body; abdominals less active on the left. Plantar flexion of the right foot, and a questionable "Babinski" on the left. Sensation: normal in all modalities. Cranial nerves: There is a questionable quadrantic defect in the left upper fields of both eyes, marked papilloedema, left greater than right. The pupils are 3 mm. in size and reacted well to light and accommodation; convergence, normal. There is a weakness of the right sixth nerve and a few nystagmoid jerks on extreme lateral gaze. The left corneal reflex is slightly diminished. There is distinct left lower facial weakness both voluntary and emotional. Other cranial nerves show no abnormality.

The course during the patient's stay in the hospital showed the following: On admission August 26, temperature, 99; pulse, 80; respiration, 18; blood pressure, 90/60. She felt dizzy when put to bed but slept well the first night. On the 28th, the patient received two doses of aspirin for headache; after a perimetric examination she complained of vertigo. On the 29th, the headache was more severe and she vomited; aspirin and soda bicarbonate gave no relief. On August 30 a lumbar puncture was done about 9:00 a.m. Some time later she vomited some yellow material and sat up several times during the day. In the afternoon she complained of severe headache over the top of her head and vomited. At 6:30 p.m. she was given 5 grains of pyramidon which she vomited and was given an ice cap to her head. She complained continually of nausea. She died suddenly at 7:00 a.m., twenty-two hours after the lumbar puncture had been performed.

The patient was under the care of Dr. Thomas K. Davis to whom I am indebted for the following additional statement "One has no grounds on which to consider the death as due to the lumbar puncture, either as a certainty or a probability. I feel that it is only a possibility which cannot be excluded. The interval between the puncture and her death was approximately twenty-two hours. Sudden unexplained death after puncture in the presence of an expanding lesion after an interval approaching twenty-four hours, is no more frequent than in the ordinary advanced case in which lumbar puncture has not been done. I consider it only a fairly remote possibility that the puncture in this particular patient brought on her death."

From a study of the hospital record, the writer had reached a conclusion which agreed with the opinion of Dr. Davis, but in fairness to this study and due to the fact the patient's course differed so greatly from that of 199 others it seems better to consider this as a probable death due to lumbar puncture.

SUMMARY AND CONCLUSIONS

This study of 200 cases in which diagnostic lumbar puncture was performed gave the following results.

1. In 94 cases of verified intracranial tumors all of them with more or less well marked signs of increased intracranial pressure of which 62

cases were supratentorial, the removal of a small amount of fluid by lumbar puncture did not give rise to any serious symptoms. Occasionally as may occur after any lumbar puncture headache became more severe for a few days, and in one case of the patient felt faint and her pulse was very rapid for a few minutes.

2. In 106 cases in which a tumor was suspected, but the diagnosis was not verified, 79 of which were supratentorial, there was one instance (G. M., reported in detail) in which serious symptoms followed the lumbar puncture and death occurred, possibly as a result of the withdrawal of spinal fluid. In the other 105 patients no symptoms of significance were caused by the careful removal of fluid from the lumbar subarachnoid space.

3. None of the patients with verified or suspected infratentorial new growths, in whom lumbar puncture was performed before the diagnosis of expanding disease in the posterior cranial fossa had been made or suspected, developed any untoward symptoms after the puncture.

Although lumbar puncture should not be done in patients with symptoms of an expanding lesion beneath the tentorium, it is of interest that in 59 cases in our series of which 32 were verified tumors in or around the cerebellum, no serious symptoms followed the withdrawal of a small amount of fluid by lumbar puncture. In most of the 59 patients, the puncture had been performed before the diagnosis of a subtentorial tumor had been made or suspected.

The study of 200 cases of brain tumor with increased intracranial pressure, has led us to conclude that in these patients, there is no danger from diagnostic lumbar puncture, if carried out with the patient in a horizontal position with a needle of small calibre, and if no more than 5 cc. are removed. If the fluid is found to be under considerable pressure, it should be allowed to escape very slowly, and the patient should always be kept flat on the back in bed for twenty-four hours.

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Section IV

METHODS FOR THE REDUCTION OF INCREASED
INTRACRANIAL PRESSURE

CHAPTER XXVIII

THE VALUE OF HYPERTONIC SOLUTIONS BY MOUTH, BY RECTUM OR BY INTRAVENOUS INJECTION FOR THE REDUCTION OF INCREASED INTRACRANIAL PRESSURE¹

FRANCIS C. GRANT, M.D.

THE effect which hypertonic solutions given by vein, mouth, or rectum exert upon intracranial tension is well known. From animal experimentation and from clinical observation, much evidence has been produced to show that by varying the osmotic pressure of the blood, the quantity of cerebro-spinal fluid recoverable from the cranial cavity can be increased or decreased. Sodium chloride, magnesium sulphate, and glucose are the hypertonic solutions most frequently employed. The effect of these substances and the duration of their action upon the cerebro-spinal fluid pressure in animals has been demonstrated by carefully controlled experiments. Clinical studies upon patients with cranial defects and observations at the operating table of the results of the administration of these solutions upon the tension existing behind the exposed portion of the brain have confirmed the findings of the experimental laboratory.

However, there has been no report of continuous observations upon humans which gives any information as to the degree of reduction of spinal fluid pressure, the rapidity with which this drop in tension occurs, or its duration. This is a preliminary report outlining a method by which continuous record of spinal fluid pressure may be made safely, without undue discomfort to the patient and the effect of the administration of hypertonic solutions can be recorded. It must be emphasized, however, that the number of patients thus studied is too small to permit acceptance of the results herein detailed as anything more than impressions requiring further confirmation.

To devise a method whereby a needle could be inserted and allowed to remain in the spinal canal in the lumbar region with perfect safety and with as little discomfort as possible to the patient was the

¹ From the Clinic of Dr. Charles H. Frazier.

first problem. The use of an ordinary lumbar puncture needle requires that the patient remain lying on one side for long periods of time. This most individuals refuse to do for they soon become cramped and restless. By the use of a German silver needle 20 cm. in length, and approximately of No. 14 gauge, this difficulty was overcome. A needle of this material can be inserted as usual with the steel stylet in place to stiffen it. The stylet is then removed and the pliable needle

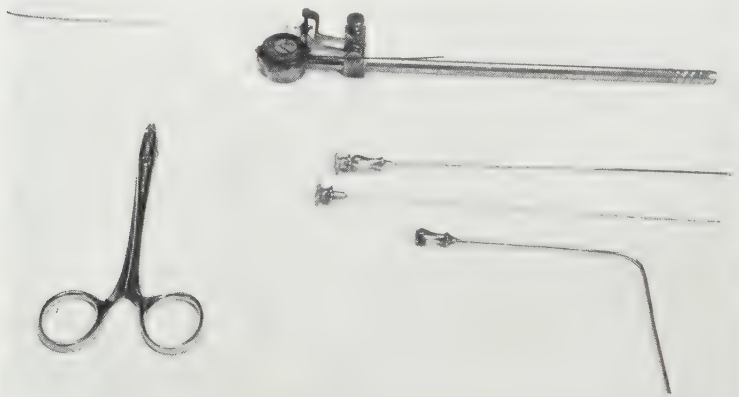


FIG. 163. Showing the complete set-up. The glass manometer and recording tambour are adjusted to the height which the spinal canal of the patient will assume when he is in the supine position. This adjustment is made by raising or lowering the kymograph table which is mounted on ratchets for that purpose. Beneath the tambour is placed the time marker. In the tubing leading to the patient are inserted four sections of glass tubing. These add rigidity and permit the operator to follow the progress of the oil globules introduced to form a barrier between the spinal fluid and the normal salt solution of the system. The dressing about the needle has not yet been applied.

is easily bent at right angles at the skin margin. Repeated experiments showed that bending a needle of this material to a right angle in even a very short curve does not collapse the lumen, for water will run through the needle after bending as freely as it would if the needle were straight. With the needle thus inserted and bent at the skin edge, the patient can lie comfortably on his back. A strip of sterile gauze is inserted between the needle and the skin and the needle is further held in place by adhesive plaster. The protruding

portion of the needle is covered with sterile gauze. This type of needle works very successfully. Once inserted it is never displaced or pulled out by any contraction of the heavy lumbar muscles or movements the patient might make in rolling from side to side. That its presence does not cause discomfort is shown by the fact that al-

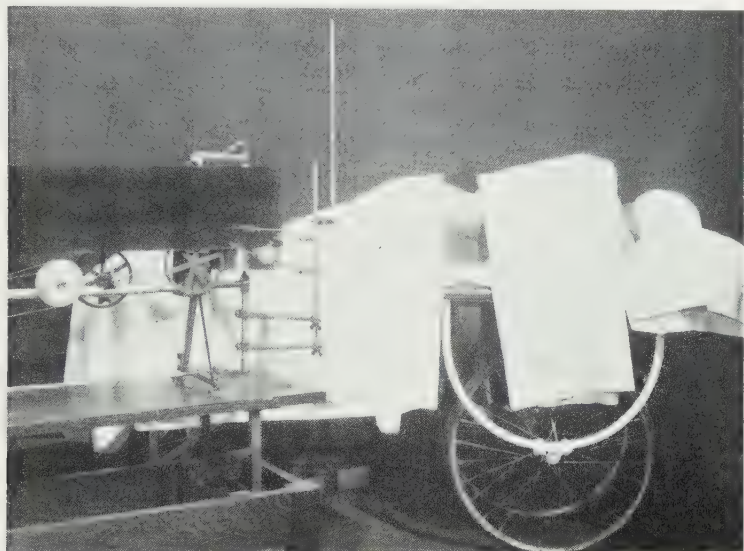


FIG. 164. Showing the special instruments necessary for the procedure. The small-sized Lombard pattern recording tambour has a very light, delicately balanced recording lever and a 19-mm. drum. It is sold by the Arthur H. Thomas Company of Philadelphia under the serial number 8046. The recording lever was made to order and not purchased with the tambour. Two special German silver lumber puncture needles 10 cm. in length and No. 14 gauge. One has the stylet in place, the other has the stylet withdrawn and is bent at a right angle. These are made to order by the George P. Pilling Company of Philadelphia. The hemostat with a groove in the blades is used for grasping and steadying the needle while it is being bent in situ.

though most of these observations were made upon adults, nevertheless, several children tolerated the needle for long periods without complaint.

As regards the relative safety of the procedure, it may be stated that continuous spinal pressure records have been made on patients for as long as 26 hours, with no demonstrable after effects beyond a slight

rise in temperature (99.3°) and moderate rigidity of the neck. These symptoms always disappear within twenty-four hours.

The needle is connected to the recording apparatus by heavy walled rubber tubing with a 2 mm. bore. In the earlier tracing this tubing was protected by a flexible hollow metal tube to prevent collapse of the tubing by the weight of the patient's body. Later experience

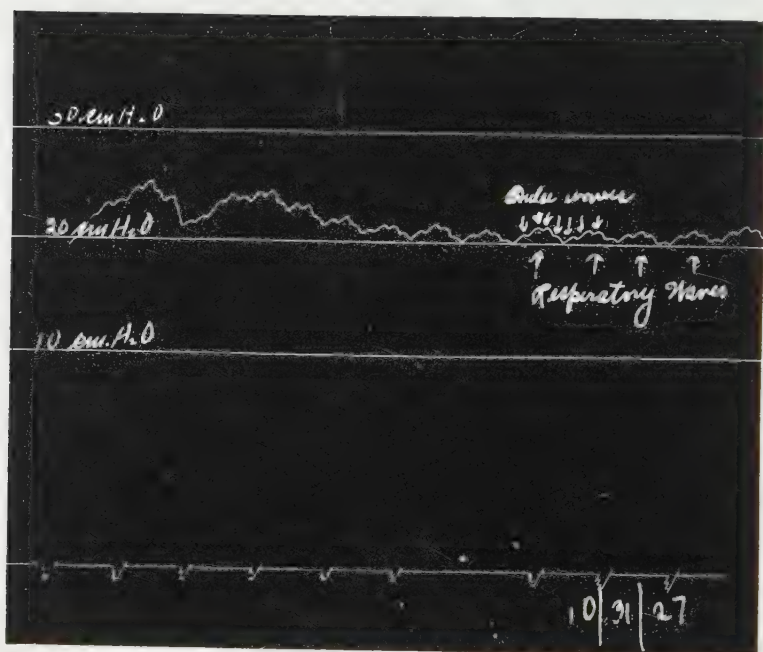


FIG. 165. Showing a typical spinal fluid pressure tracing taken at a speed of 12 cm. per minute. The lowest line represents the time in five-second intervals. Note the pulse and respiratory waves which illustrate the quick response of the recording lever to the slightest movement of the fluid.

showed this metal protection to be unnecessary as the patient's body and the mattress upon which he lay were both so soft that collapse of the tube did not occur even if he rolled over on it.

The tracings are made by means of a small tambour covered with condom rubber recording by a long lever on a smoked drum. This drum carries a twelve foot paper, so geared that it can be run as slowly as 24 cm. an hour. A glass T-tube leading to a water manometer such

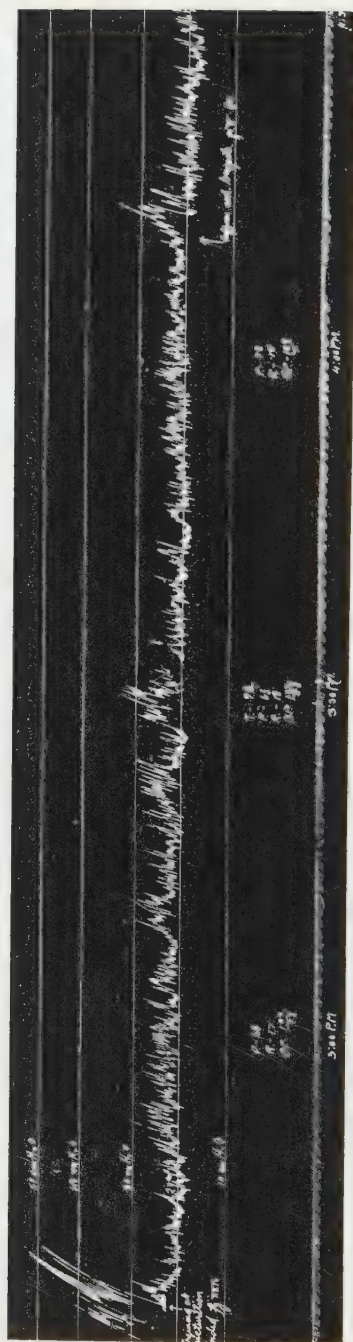


FIG. 167. This tracing illustrates the type of variations encountered in a slightly nervous patient. Duration of tracing two hours. Rate of drum 24 cm. per hour.

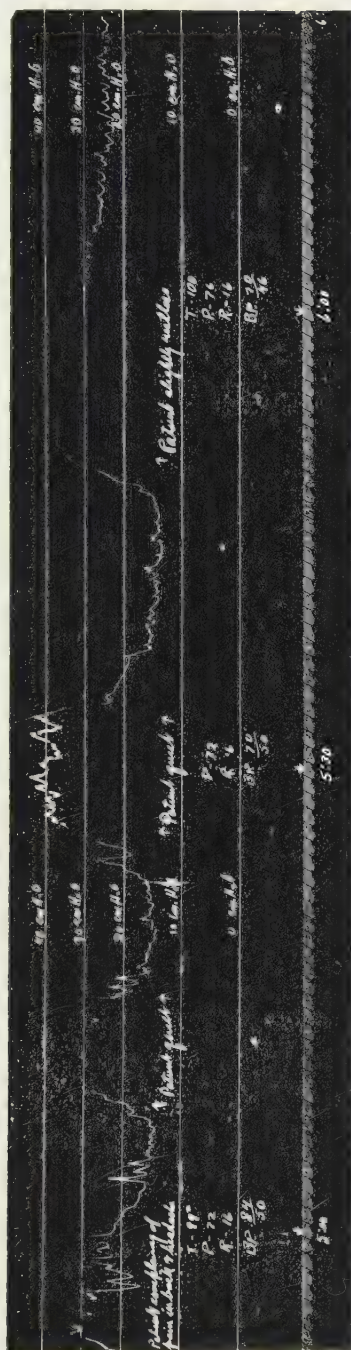


FIG. 168. This patient was a boy of fifteen years who had a calcified hypophyseal duct tumor. The tracing illustrates the remarkable rises in pressure which occur at times in some subjects with nothing to explain them. In this case, the pressure on two occasions rose from 150 to 400 mm. of water while the patient was apparently physically and mentally composed. Rate of drum 24 m. per hour.

as is ordinarily used for making lumbar puncture pressure readings is inserted in the system between the needle end and the recording tambour.

The technique of setting up the apparatus is as follows: The needle, glass manometer, T-tube and rubber tubing connections are sterilized by boiling; the tambour by immersion in 70 per cent alcohol for thirty minutes. The patient's back is prepared as usual for lumbar puncture. The rubber tubing, water manometer, and tambour are filled

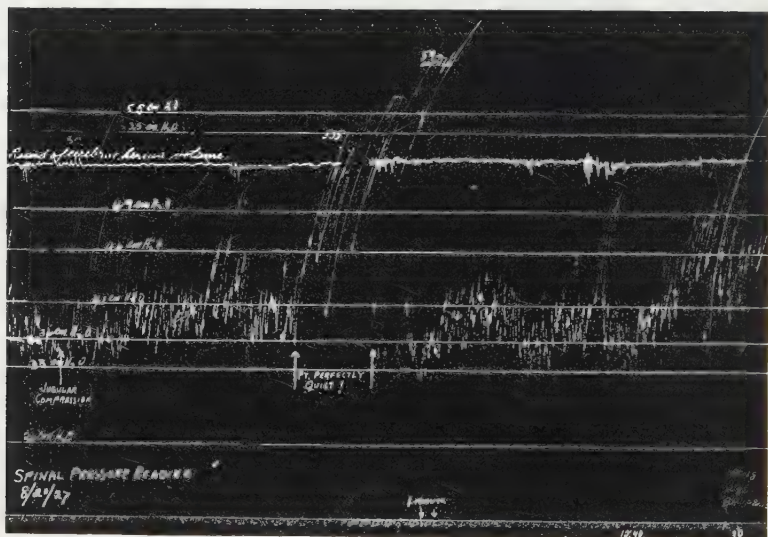


FIG. 169. This patient was a boy of eight years who had received a severe cranial injury twelve weeks previously, resulting in a communicating hydrocephalus. Note the unexplained rise in pressure from 360 mm. of water to 590 mm. Rate of drum 24 cm. per hour.

with sterile normal saline, great care being taken to see that all air bubbles are excluded. The fluid is drained from the manometer down to the zero point and that end of the tubing to be connected to the spinal needle is clamped off with a hemostat. The tambour and water manometer are then attached to the recording stand, as shown in the illustration. The needle with its stylet in place is then inserted into the fourth or fifth lumbar interspace. The stylet is withdrawn and if spinal fluid appears, the tubing is promptly connected and the hemostat removed from it.

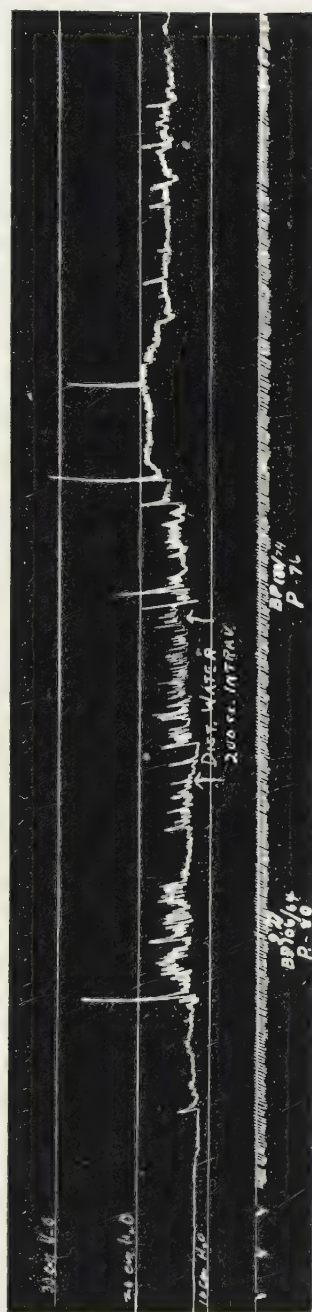


FIG. 170. This is the tracing of a patient with brain tumor and a pressure of 175 mm. of H_2O in whom the administration of 200 cc. of distilled water intravenously caused a rise in pressure of 20 mm. of H_2O within ten minutes. This rise, however, was maintained only for about eight minutes after which a gradual return to the initial pressure occurred. Rate of drum 24 cm. per hour.

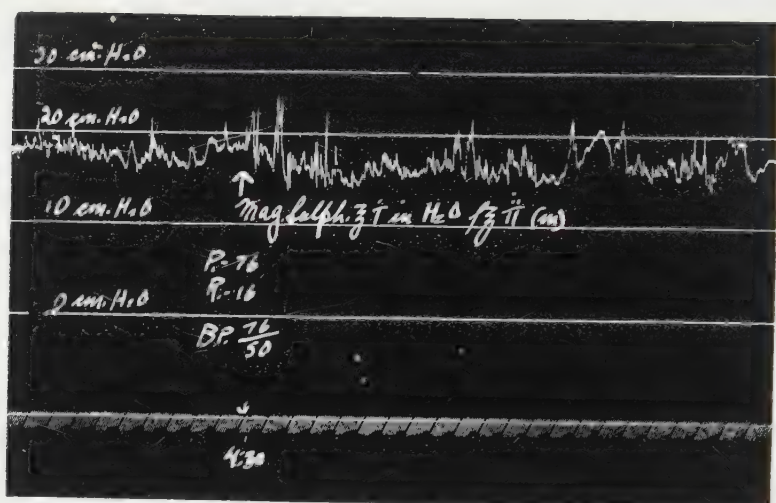


FIG. 171. A case of slightly increased pressure (180 mm. H_2O) due to brain tumor. This patient showed an early but slight drop (20 mm. H_2O) in spinal fluid pressure following the administration of magnesium sulphate by mouth. This drop was scarcely maintained during the twenty-two minutes represented by the portion of the tracing shown. The drum was moving at the rate of 24 cm. per hour.

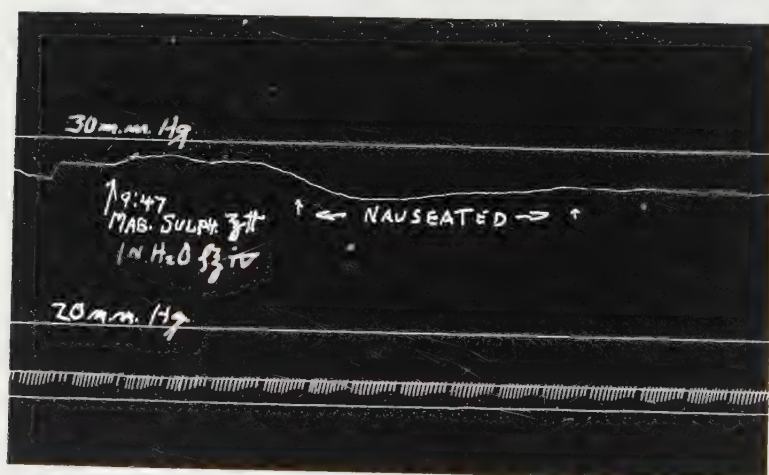


FIG. 172. A patient with Jacksonian epilepsy and increased spinal fluid pressure in whom no tumor was found at operation. Note the drop from 29 mm. Hg. to 27 mm. Hg. due to nausea following the administration of magnesium sulphate by mouth. This was one of the earlier tracings, made before certain refinements were introduced into the technique. Rate of drum 54 cm. per hour.

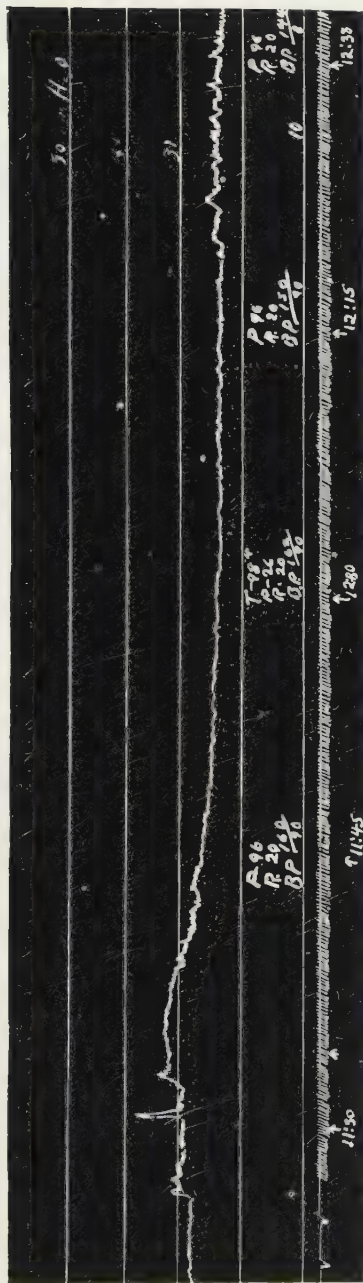


FIG. 173. Tracing of a patient partly dazed, the result of cranial trauma, in whom therefore most psychic stimuli were excluded. Note the rise from 290 mm. H_2O to 325 mm. H_2O occurring two minutes after the intravenous administration of hypertonic glucose and maintained for six minutes, followed by a gradual fall to 235 mm. of H_2O . This represents a drop of 55 mm. of H_2O . The pressure reached its lowest level thirty minutes after the administration and was maintained for one hour and twenty minutes at which time magnesium sulphate was administered (see next tracing). Rate of drum 24 cm. per hour. Note the steadiness of pulse and respiratory rates and the relatively slight variations in blood pressure.

The needle is then grasped with the grooved hemostat and bent to a right angle snugly against the skin, the end connected to the tubing being swung at right angles to the spine across the lumbar muscles. The needle is secured in place with gauze and adhesive as described. The patient is then rolled on his back and told to make himself comfortable. Meanwhile, the tambour and water manometer are adjusted as closely as possible to the level of the spinal canal of the subject being tested. If the system is working properly, both the record-

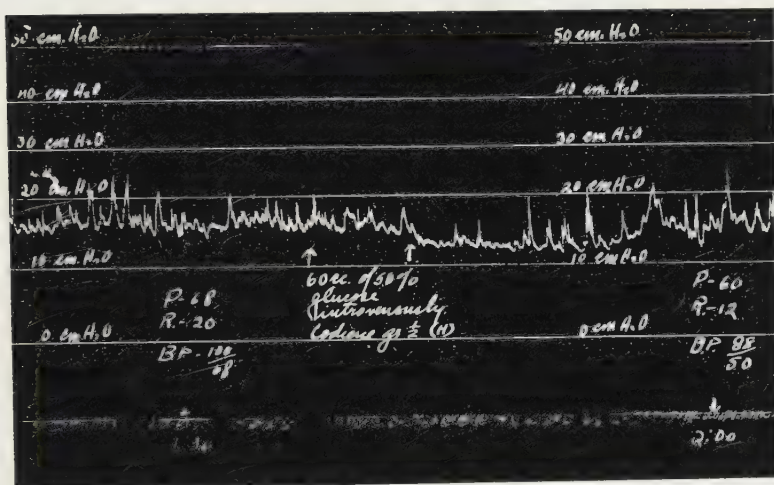


FIG. 176. A patient with brain tumor and practically a normal spinal fluid pressure (160 mm. H₂O). Illustrating a quick but slight response to hypertonic glucose administered intravenously. The drop of 35 mm. occurred within two minutes but was maintained for less than fifteen minutes. Rate of drum 24 cm. per hour.

ing needle of the tambour and the fluid in the manometer will oscillate with each heart beat and respiratory excursion. If this occurs, the drum is started and the tracing recorded. In this way, the spinal fluid pressure at any moment may be read on the manometer while a continuous tracing of the pressure is being recorded on the smoked paper. The time intervals are also recorded on the paper by means of a watch timer. When the tracing is complete, it is calibrated by drawing lines the entire length of the tracing for every 50 or 100 mm. of water pressure.

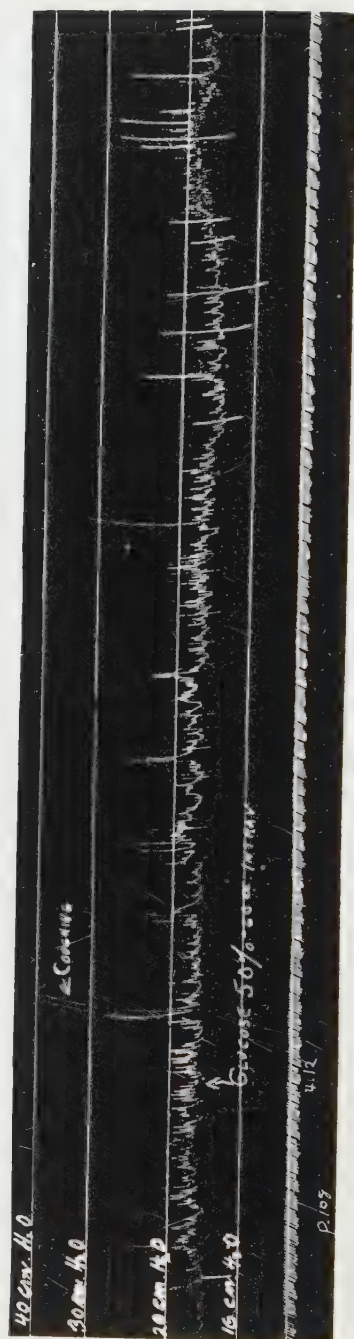


FIG. 177. This illustrates the slight effect of hypertonic glucose in a case of slightly increased intracranial pressure. The initial pressure was 185 mm. H_2O . Forty minutes after the introduction of 60 cc. of 50 per cent glucose intravenously it had only fallen to 180 mm. of H_2O —a difference of 5 mm. of H_2O , and this was maintained for only about ten minutes. Rate of drum 24 cm. per hour.

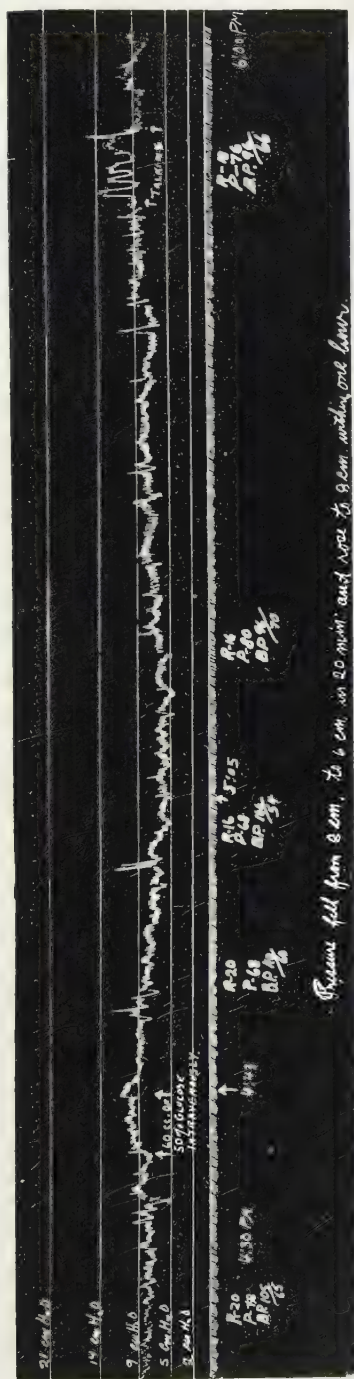


FIG. 178. This tracing illustrates the effect of a hypertonic solution in a case with a low normal spinal fluid pressure. The initial pressure was 80 mm. of water, rose to 100 mm. during the course of the introduction of 60 cc. of 50 per cent glucose and fell to 60 mm. within twenty minutes. Following which it returned to the initial reading within one hour. Rate of drum 24 cm. per hour.

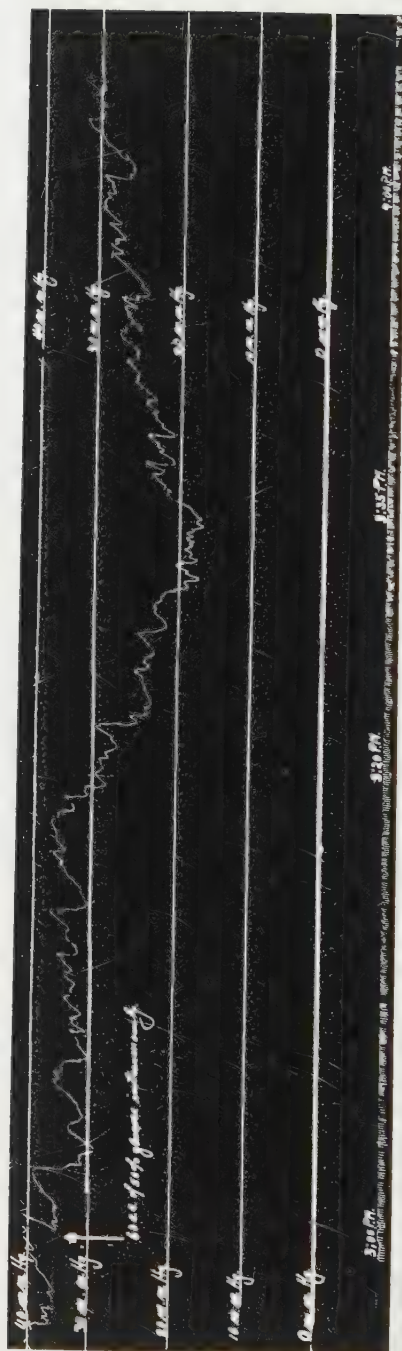


FIG. 179. This is one of the earlier tracings on a patient with a large brain tumor of the left temporal lobe. Note the fall in pressure from 40 mm. to 20 mm. of mercury occurring thirty minutes after the administration of 60 cc. of 50 per cent glucose intravenously. The pressure in this case returned almost to the initial reading seventy minutes after the administration. Rate of drum 45 cm. per hour.

Further use of this apparatus brought to light a number of technical difficulties. In the first place, long continued insertion of a needle produces a sterile meningitis, an increased cell count and a gradual rise in pressure. Especially is this so if the normal salt solution used to fill the system be allowed to mix freely with the spinal fluid. To prevent this admixture of the normal salt solution and the spinal fluid, 1 or 2 cc. of sterile paraffin oil is injected into the rubber tubing about 10 cm. from the needle by means of a hypodermic syringe. This forms a barrier between the spinal fluid and the normal salt solution in the system, and in great measure prevents the cellular exudation and gradual increase in pressure.

Perfect coöperation on the part of the patient is essential. He must lie entirely quiet. The slightest movement of any extremity is followed by a rise in cerebrospinal fluid pressure. Most extraordinary variations in tension occur even in the absence of any observable degree of motion. Coughing, straining, or the passage of urine, flatus, or feces is shown promptly by a rise of the recording lever. The accompanying tracings (figs. 163-164) fully illustrate these points.

Magnesium sulphate was given in 2 or 4-ounce doses of a 50 per cent solution by mouth, and glucose by vein in a 50 per cent solution usually 60 cc. in amount.

The tracings obtained show that under conditions of perfect coöperation the spinal fluid pressure maintains itself at a given level for long periods of time, or may exhibit a slow steady rise due we believe to the aseptic reaction to the presence of the needle. The action of hypertonic solutions seems in direct proportion to the intracranial pressure at the time of their administration; if the pressure is low they cause little or no drop in its level; if it is raised, an appreciable drop follows their use. Any reduction in tension they cause is prompt but relatively transient, seldom lasting for more than an hour after which the pressure returns slowly to its original level. We never saw it return to a higher level.

The effect produced by 50 per cent glucose by vein seems rather greater and more sustained than that following magnesium sulphate by mouth. However, the number of tests conducted is too few to gain more than an impression of the relative effectiveness of these solutions. Further experiments with this apparatus are being made which may correct the opinions at present held. However, it is be-

lieved that the technique outlined affords us a practical means whereby continuous direct records of spinal fluid pressure over long periods of time can be made in safety without discomfort to the patient, and allows the accurate testing of the effect of hypertonic or hypotonic solutions upon the intracranial tension in the human subject.

CHAPTER XXIX

THE EFFECT OF SUBTEMPORAL AND SUBOCCIPITAL DECOMPRESSIVE OPERATIONS IN IRREMOVABLE TUMORS OF THE BRAIN AS REGARDS THE RELIEF OF HEAD-ACHE, THE PRESERVATION OF VISION AND THE IMPROVEMENT OF PARALYSIS

GEORGE J. HEUER, M.D.

THE subtemporal and suboccipital decompressive operation have long held a place in the armamentarium of the neurosurgeon. Like many other operations in surgery they have often been indiscriminately used and the results obtained not always those which had been anticipated. Like other operations, too, they have been retained nevertheless as useful procedures by certain men, almost discarded by others. Before attempting to evaluate them in the treatment of irremovable brain tumors it might be well to consider them and what they may be expected to achieve as well as the conditions for the treatment of which they are commonly used.

The subtemporal and suboccipital decompressive operations for our present purpose are mechanical procedures designed to reduce an increased intracranial pressure due directly or indirectly to brain tumors. They are far from perfect procedures. Were the cavity within the skull a single chamber and the intracranial contents a simple semi-fluid mass, then it might be expected that an opening in the skull and dura if sufficiently large would permit the escape of the semi-fluid mass in an amount proportional to the pressure and so reduce and maintain the pressure at normal. But as is well known the matter is not so simple as this and various factors may operate against the success of the procedure. These may be enumerated as follows: (1). The intracranial cavity is not a single cavity but is subdivided into an anterior and posterior cavity by the resistant and more or less inelastic tentorium. The anterior chamber further, is partially subdivided into a right and left cerebral cavity, by the falx. These partitions within the skull cavity, while they do not prevent the distribution of pressure, yet they do, to a certain extent, prevent the *equal*

distribution of pressure. The greatest pressure due to a tumor, if unassociated with an internal hydrocephalus, is clinically for a time at least exerted in that subdivision of the intracranial space which harbors the tumor.¹ All other considerations being for the moment disregarded, the greatest relief from pressure is obtained by a decompressive operation over this subdivision. The question of accurate diagnosis, then, influences the success of decompressive procedures; and failure to place properly a decompressive defect in the skull, has in our experience as in that of others, influenced detrimentally the success of the procedure.

(2). Perhaps the first effect of increased intracranial pressure is a venous stasis, which results from the failure of a free outflow of the venous blood. Of itself it may be the cause of widespread disturbance such as cerebral edema and papilloedema and far outweigh the tumor itself as a cause of pressure. It is often relieved by decompressive measures; but it may, because of cerebral dislocation or other unknown factors, not only not be relieved by operation, but definitely increased and lead to the death of the patient. So far as I know, we cannot predict the latter complication.

(3). The brain is subject occasionally to rapid changes in volume, due to edema, either the result of manipulation or to venous stasis or to the pressure of a tumor. Venous stasis which we have just considered, does not always appear to be the cause. Although seen less frequently than formerly, due perhaps to a more careful technic, we still occasionally see a rapidly developing cerebral edema which quite defeats our operative procedure.

(4). The ventricular system of the brain may become obstructed or occluded by the tumor and the resulting internal hydrocephalus far outweigh the tumor as the cause of the increased intracranial tension. A decompression in the presence of an internal hydrocephalus is effective only if it relieves ventricular obstruction. Since internal hydrocephalus is more often associated with a posterior fossa tumor, a suboccipital decompression will often so change conditions, that ventricular obstruction is relieved. But this is not always the case; and it sometimes happens that the obstruction is either not relieved or because of cerebral dislocation is actually increased. Internal hydrocephalus may be due also to a cerebral rather than a posterior fossa

¹ Recent experiments on the dog, by Cook and myself, would indicate that this is not true of the cerebral cavity in the dog.

lesion—as in the tumors about the infundibulum. In such a case a subtemporal decompression does not relieve the pressure any more than it relieves that due to a posterior fossa tumor; for the ventricle simply dilates to occupy the additional space afforded by the decompression. Here also a decompression may make conditions worse and in a recent case of proved irremovable infundibular tumor associated with internal hydrocephalus, the operation which terminated in a decompression undoubtedly increased rather than diminished the intracranial tension. Internal hydrocephalus in irremovable tumors, therefore, is a serious complication from a therapeutic standpoint. The decompressive operation must be correctly placed over cerebrum or cerebellum to expect any relief at all; but in a certain number of cases, even if correctly placed, it will fail to reduce to any considerable degree the increased intracranial tension.

(5). The tumor itself particularly the gliomas and cystic gliomas, may defeat at times the purpose of the operation. Sudden and large or slow hemorrhage into a tumor has occurred, I imagine in the experience of most of us. The complication may occur soon after the operation and we find that instead of relieving the pressure symptoms these are definitely increased. The patient may die with pressure symptoms and show at autopsy a large fresh hemorrhage into the tumor. Or the patient may be relieved of his pressure symptoms for a variable period and then quite suddenly have a marked increase in his symptoms. Should he die, autopsy will sometimes reveal a large hemorrhage into the tumor. The cause of such hemorrhages is not always clear; no more than it is clear in tumors elsewhere in the body. By those who oppose decompressive operations, the suggestion has been made that the withdrawal of support, as in a decompression, favors hemorrhage into a tumor and probably this sometimes is a factor.

Having pointed out some of the factors which at times operate against the success of the subtemporal or suboccipital decompression, let me briefly discuss the symptoms for the relief of which they are commonly performed. We are concerned in this discussion particularly with headache, nausea and vomiting, failure of vision and paralysis. It is obvious that these symptoms may be produced in at least two ways—either by pressure upon or distension of structures or by involvement with destruction of structures. *Headache* is probably most often the result of increased intracranial tension, for so often at operation or autopsy there is no evidence of direct involvement of

the dura or other structure. On the other hand, I, as no doubt many of you, have observed headache in patients in whom there was no increased intracranial pressure but direct involvement of the dura—as in lues and small endothelioma. *Nausea and vomiting* are also in the majority of instances manifestations of pressure; but may, as in tumors involving the pons, occur in the absence of increased pressure. *Impairment of vision* in association or not with choked disc is often purely a pressure phenomenon, for the relief of pressure will promptly restore vision; on the other hand, it may be due to destruction or atrophy of the visual centers in the brain or of the fibers of the optic pathway. It may follow upon and be in consequence of increased intracranial pressure in association with choked disc; or it may result from optic atrophy in the absence of choked disc. One of the great disappointments in neuro-surgery is the failure to restore vision; but it must be evident that decompressive operations can restore vision only when the impairment of vision is due to an interruption of visual fibers in consequence of local or general increased intracranial pressure and fails to restore vision when loss of vision is due to destruction of visual centers or atrophy of visual fibers. *Loss of function*, paresis or paralysis may be again the result of pressure upon structures or to destruction of centers or nerves; or possibly in part to both. You are all familiar for example with loss of smell in cerebellar tumors, a pure pressure phenomenon which promptly disappears with the relief of intracranial tension; or the palsy of the sixth nerve or of an extremity. On the other hand, loss of function may be due to destruction of brain substance or to nerve pathways. Just as in impairment of vision, it is often difficult and even impossible to tell which factor is operative, so in paralysis it often cannot be determined even at the operating table whether a given palsy is due to pressure or to destruction of tissue. Examples may be given at length but must be familiar to you. I quote one or two in my own experience as illustrations. A simple dural endothelioma or meningioma over the motor strip in a patient with a palsy of the leg is removed. It has made a nest for itself by indentation of the cortex but has not involved the cortex except by pressure. It is simply lifted out of its nest without hemorrhage. Here the palsy is apparently purely a pressure phenomenon; and although the patient recovers and is living for over ten years, the palsy persists. In this instance a benign, non-invading tumor has produced an atrophy of motor cells or fibers which is permanent. Again we expose an

infiltrating glioma of the motor cortex associated with a palsy. We decide we cannot remove it and do a decompressive operation. To our gratification the paralysis, which we thought was due to a destructive process, largely disappears—as evidence that it was due to pressure. Similar observations have been made in diffuse gliomatous involvement of the cord with paraplegia. These are instances of invasive destructive tumors producing their effect by pressure or edema. Just as in impairment of vision associated or unassociated with choked discs, we cannot certainly predict the nature of the palsy until we observe the results of our operative procedures.

From this discussion of the factors which may operate against decompressive operations and of the causes of the symptoms which they are expected to relieve, it must be apparent that the subtemporal and suboccipital decompressive operations are at best uncertain procedures and may be expected to relieve symptoms in only a certain proportion of cases. Not only may they fail because of one or several of the factors above enumerated, but it is stated by some to have definite objections. We have stated that they may be followed by death, soon after operation, due to sudden cerebral dislocation or to an acute cerebral edema or to hemorrhage into a tumor or ventricle; but in addition to this danger, they are said to be the cause of a more rapid growth of the tumor and if they bring relief, it is but for a short period of time. The question whether or not a decompressive operation causes a more rapid growth of the tumor, is indeed a difficult one to answer. It might well be supposed that the relief of pressure would favor growth by lessening the resistance to growth. We do not believe this is the case. Yet so many factors enter into the matter that no data which I have been able to assemble serve to establish the matter. To compare the duration of life from the onset of symptoms to death of two groups of cases, one subjected to operation the other not, leaves out of consideration so many factors as to be in our opinion valueless. *The duration of relief* which decompressive operations offer is again variable. If relief is obtained, this relief as a rule becomes apparent soon after operation; and its continuance is subject to many factors. The rate of growth of the tumor is one important consideration. We have observed for ten years, two cases in which a tumor was seen at operation but not removed. Complete relief of pressure symptoms followed simple decompressive operations. For unknown reasons the tumor ceased to grow and slowly underwent calcification.

At the end of ten years the x-rays showed the shadows of the calcified tumor; and the cerebral herniae which followed the decompressive operation were no larger ten years after operation than ten months after operation. On the other hand a tumor may slowly grow and with it the cerebral hernia. Symptoms may be relieved for months or even years; and death may eventually occur not the result of pressure symptoms but because of the involvement of vital cerebral centers. Or, after a lapse of time, during which pressure symptoms have been quiescent, these gradually or suddenly reappear, either due to a more rapid growth of or hemorrhage into the tumor or to the filling of a cyst; or to the fact that the decompressive opening is no longer effective because of adhesions to the margin or resistance of overlying soft parts or to the development of an internal hydrocephalus. If pressure is not relieved again, death occurs with pressure symptoms. With our minds then open to the many disadvantages under which these procedures labor, let us go on to study, so nearly as we can, their effects as regards the relief of headache, the preservation of vision and the improvement of paralysis.

In a series of 828 cases of brain tumor which I studied some time ago with reference to the immediate and late results obtained by surgical efforts, I divided the number into verified, those in which the tumor had been seen at operation or necropsy, and unverified or presumed, those in which a diagnosis of tumor had been made but the lesion not disclosed at operation. There were in the series of 485, or approximately 60 per cent, verified tumors and 343, or 40 per cent unverified or presumed tumors. The two groups of cases were further subdivided according to the known or presumed location of the lesion, *i.e.*, into verified and presumed cerebral, hypophyseal, cerebellar, cerebello-pontine angle and brain stem tumors. In our present study we shall adhere to this gross classification and try to determine the effects of decompressive operations in these groups. We shall consider only such cases in which a decompressive operation alone was done and exclude all cases in which even a partial removal of the lesion was attempted. To do so will militate against the results of decompressive operations for it will exclude many favorable cases in which obviously the decompression was the significant procedure; the removal of a small fragment of what really was an inoperable tumor constituting an insignificant step in the operation.

VERIFIED CEREBRAL TUMORS

There were 250 cases of *verified cerebral tumor* of which 243 were subjected to operation. In 78 of these 243 cases a decompressive operation was the only therapeutic measure although in many instances the operation began with an exploration in the hope of finding and removing the lesion. In a certain number of cases the lesion was not disclosed at operation; in perhaps an equal or larger number it was disclosed but considered inoperable. In 63 cases the operation consisted of a single subtemporal decompression; in 1, a bilateral subtemporal decompression; in 7 a subtemporal and suboccipital decompression; and in 4 a suboccipital decompression alone. In 4 cases the removal of a bone flap used for exploration constituted the decompression. In the 11 cases in which a suboccipital decompression was done it was performed either because of a mistaken diagnosis or because the subtemporal operation failed to bring relief. Of these 78 cases 23 died in one month or less and therefore may be excluded from our summary even though in this brief period they may have had relief from their pressure symptoms. When we examine these 23 deaths we find that some of them were due to causes previously discussed as operating against the decompression. One death occurred the day of operation due to an acute hemorrhage into the tumor; 1 of acute cerebral edema; and 3 of internal hydrocephalus. Two other deaths occurred promptly following misplaced decompressive operations in the suboccipital region. Of the remaining deaths 1 occurred from respiratory paralysis following a lumbar puncture, 1 a decompression in a patient unconscious for two weeks before operation and 1 from post-operative pneumonia. Three deaths occurred in patients with multiple carcinomatous or sarcomatous metastases.

Of the 55 cases which survived more than one month 22 *lived or were living from one month to six months*. In 10 of these there could not be said to have been any considerable improvement as a result of the operation. In the remaining 12 there was definite and often marked improvement as indicated by the relief of pressure symptoms. Headache and vomiting disappeared or was greatly relieved and choked disc subsided with improvement in vision in those not already blind. Paralysis however were but slightly if at all improved. In this group internal hydrocephalus, proved at autopsy, was the probable cause of the failure of the decompressive operations in 2 cases; a mis-

placed decompression in the suboccipital region in a tumor of the parietal region was the probable cause of failure in 1 case.

Nine patients lived from six months to one year. In 2 cases there was little if any improvement; in 6 there was great improvement in or complete relief from the pressure symptoms. In 1 of these with paralysis of the extremity, the paralysis one year after operation had definitely improved but had not disappeared. In 3 cases in this group a second operation with removal of the tumor was performed from seven months to one year after the primary decompression. In these, complete relief of pressure symptoms occurred in the interval between the primary and secondary operations; an advantage of the decompressive operation which should be emphasized.

Seventeen patients lived or were living from one to twelve years after operation. Of these 13 had lived or were living from one to three years; 4 had lived or were living from four to twelve years. In the group of 13 living from one to three years, 6 were subjected to secondary operation for the removal of the tumor from one to three years after the primary operation. Four died after the second operation; 2 lived and reported themselves as well three and five years after the second operation; although 1 blind on admission remained so. In the group of 4 living from four to twelve years there were no secondary operations. With regard to the effect of decompressive operations in these 17 patients it may be said almost without exception that the pressure symptoms were markedly if not completely relieved during the life of the individual. In 2 with marked impairment of vision or complete blindness on admission vision was not restored or greatly improved. In two admitted with paralysis of the extremities, the paralysis was not improved one and one-half to two years after operation. It is of interest to know the type of lesion in the 4 cases which lived from 4 to 12 years. Two were proved endotheliomas or neurofibromas, 1 a syphiloma, and 1 a cystic glioma.

To sum up the group of verified cerebral tumors:

(1) Of 243 cases subjected to operation, in 78 a decompressive operation was the only therapeutic measure.

(2) Twenty-three of the 78 cases died within one month of operation and of these 1 died of acute hemorrhage into the tumor, 1 of acute cerebral edema, 3 of unrelieved internal hydrocephalus and 2 following misplaced decompressive operations.

(3) Twenty-two lived from one to six months and of these 10 were

unimproved and 12 markedly improved as regards their pressure symptoms.

(4) Nine lived from six months to one year and of these 2 were unimproved, 7 markedly improved.

(5) Seventeen lived or were living from one to twelve years all markedly improved.

(6) In 7 cases the end result of the therapeutic operation is not known.

(7) A review of these cases shows that headache, vomiting and choked disc are commonly relieved. Vision is improved or not depending upon the absence or presence of advanced optic atrophy. Paralysis in this series was improved only once; was not improved in the majority of cases.

VERIFIED HYPOPHYSEAL TUMORS

Of 74 verified hypophyseal tumors in our series 72 were subjected to operation. In 23 of these a decompressive operation constituted practically the only therapeutic measure, and it is unnecessary to remark that these were advanced cases with general pressure symptoms. In 7 of the 23 cases a sellar decompression through a transphenoidal approach was the only decompressive measure used and these cases are therefore excluded as not germane to our discussion. In 16 cases a subtemporal decompression alone or a subtemporal and sellar decompression were employed. In 9 cases a subtemporal decompression alone was used. Four died within a few days to two and one-half months unimproved. One lived six months considerably improved. Four lived or were living from six to eleven years. Of these one was blind but otherwise perfectly well earning her livelihood by basket making; 3 had impaired vision or blindness and continued to have headaches. In 7 cases a subtemporal decompression was preceded by an unsuccessful sellar decompression or followed by a transphenoidal operation with the purpose of removal of the tumor terminating however in a sellar decompression. Three died in 1 year or less unimproved in these symptoms. Four lived from three and one-half to eight years. Of these all were definitely improved as regards the relief of headaches, and in 3 instances there was improvement in vision. One patient was blind and remained so.

To sum up the group of verified hypophyseal lesions:

(1) Of 72 cases subjected to operation, in 16 a subtemporal decom-

pression alone (9) or a subtemporal and sellar decompression were the only therapeutic procedures.

(2) Eight cases died a few days to one year after operation with definite and considerable improvement in symptoms in only 1 case.

(3) Eight cases lived from three and one-half to eleven years—the majority over six years—and of these 5 were markedly improved as regards the relief of headaches, 3 continued to have occasional headaches; 3 had improvement in vision; 3 had markedly impaired vision and so continued and 2 were blind and remained so.

VERIFIED CEREBELLAR TUMORS

Of 86 verified cerebellar tumors, 85 were subjected to operation. In 25 of these a decompressive operation, suboccipital or subtemporal, was the primary therapeutic effort made. In 6 of the 25 cases a subtemporal decompression was the primary operative procedure and performed presumably because of uncertainties in diagnosis. Five of these patients died from a few hours to one month after operation, and at autopsy showed an unrelieved internal hydrocephalus. There was no evidence of improvement during life. One patient lived one and one-half years after a subtemporal decompression undoubtedly relieved of his symptoms; at the end of which time a suboccipital decompression was performed. He lived two years after this procedure again in comparative comfort; then died following a third operation in which the tumor was removed.

In one case a *sellar* decompression was performed on a patient who had developed headaches and acromegaly and whom cerebellar signs were not prominent. He died 3 days after operation and at autopsy a large cerebellar cyst was disclosed.

In 18 cases a primary suboccipital decompression was performed. In 14 of these a suboccipital decompression alone was done. Of this group 5 died from one to sixteen days after operation. These were desperate cases with advanced pressure, some in coma. Autopsies showed an internal hydrocephalus. Five lived from six months to one year and of these 1 was unimproved, 4 were greatly relieved. In these headaches and vomiting were quite relieved and vision was improved in all excepting one. Three lived or were living five and one-half to nine years. Of these all were entirely relieved of their symptoms. Their headache and vomiting disappeared and their vision improved or returned to normal. In 1 the only residual symptom

was occasional vomiting. In one of the 14 cases the result is not known.

In 4 of the 18 cases a suboccipital decompression was followed some time later by the evacuation of a cyst or the attempted removal of a solid tumor. In 1 a suboccipital decompression quite relieved the pressure symptoms for two years which then returned. At a second operation the tumor was removed but the patient died some time later. In 1 case a suboccipital decompression relieved symptoms for three months with improvement in vision, at which time a cerebellar cyst was evacuated. This patient was living when last heard from 15 years after operation and was entirely well. In 1 case a suboccipital decompression was followed one and one-half years later by the evacuation of a cyst and three and one-third years later by a third operation. In the one and one-half year interval between the decompression and the cyst evacuation he was relieved of his pressure symptoms. He died following the third operation. In the fourth case a suboccipital decompression was followed three years later by the evacuation of a cyst. In the three year interval he was relieved of his pressure symptoms, and was living and well excepting for an occasional headache four and one-half years after operation.

In the group of cerebellar tumors paralysis of a major type is not common. Incoördination as manifested by staggering gait on the other hand is common. It is to be remarked that some incoördination persisted in the majority of cases.

To sum up the group of verified cerebellar tumors:

(1) of 85 cases subjected to operation, in 25, a decompressive operation was the primary and in the majority the only therapeutic procedure.

(2) In 6 of 25 cases a subtemporal decompression, performed because of uncertainty in the focal diagnosis, was done. Five of the 6 promptly died unrelieved of or with an increase in their symptoms. One lived one and one-half years relieved of his pressure symptoms.

(3) In 1 of the 25 cases a sellar decompression was performed because of mistaken diagnosis. The patient promptly died showing at autopsy a cerebellar cyst.

(4) In 14 of the 25 cases a suboccipital decompression alone was done. Five cases in advanced stages of pressure died in one to sixteen days. Five lived from six months to one year of which 4 were relieved of their symptoms. Three lived or were living five and one-

half, nine, and nine years, respectively, practically well at the time of the last report. One was not heard from.

(5) In 4 of the 25 cases a suboccipital decompression was followed in three months, one and one-half years, two years and three years, respectively, by the attempted removal of the lesion. In all the patients were relieved in the interval between the decompression and the secondary operation.

VERIFIED CEREBELLO-PONTINE TUMORS

There were 40 cases all subjected to operation. In 15 of these a suboccipital decompression (in 1 case a subtemporal) was the primary and in 10 of the 15 the only surgical procedure. Of the 10 cases in which a suboccipital exploration and decompression was the primary and only operation 8 died within a month, the majority dying within twenty-four hours. Of these 3 died on the operating table or immediately afterwards of respiratory paralysis. Of the 2 cases which recovered 1 died an indefinite period after operation with the pressure symptoms somewhat relieved; 1 was living four years after operation unimproved with persistent headaches, failing vision and increasing incoördination.

In 4 cases a suboccipital decompression was followed after a short interval by an attempted removal. Three cases died after the second operation one from meningitis. One recovered and was living and practically well twelve years after operation. In these 4 cases the interval between decompression and removal was short (from one to ten months) but in this interval 2 were improved and 2 unimproved.

In 1 case a subtemporal decompression was followed nine months later by a suboccipital decompression. The patient died twenty-five days after the second operation and the autopsy showed an internal hydrocephalus. In the nine months interval the patient was not improved.

To sum up the group of verified cerebello pontine angle tumors:

(1) Of 40 cases subjected to operation, in 15 a decompressive operation was the primary surgical operation.

(2) In 10 of the 15 cases a suboccipital decompression was the only surgical procedure used. Of these 9 promptly died, 1 was living but unimproved four years and 1 was improved for an indefinite period.

(3) In 4 cases a suboccipital decompression was followed in from one to ten months by an attempted removal of the tumor. Three

patients died; 1 recovered and was practically well twelve years after operation. In the short interval between the decompression and the second operation 2 were improved, 2 unimproved.

(4) In 1 case a subtemporal decompression was followed nine months later by a suboccipital decompression. The patient died twenty-five days after the second operation and the autopsy showed an internal hydrocephalus. In the nine months interval the patient was not improved.

VERIFIED BRAIN STEM TUMORS

Of 33 verified brain stem lesions subjected to operation a subtemporal or suboccipital decompressive operation was the primary and only important therapeutic procedure in 23. In 6 of the 23 cases a subtemporal decompression was done. All died in from twenty-four hours to nine months unimproved. One patient who died with hyperpyrexia showed at autopsy an enlarged persistent thymus. In 17 of the 23 cases a suboccipital decompression was done. Sixteen died in from twenty-four hours to six months unimproved. One was discharged from the hospital unimproved but the end result is not known.

To sum up the group of verified brain stem tumors:

(1) Of 33 cases subjected to operation a subtemporal or suboccipital decompression was the primary and only important operation in 23.

(2) Of the 23 cases a subtemporal decompression was done in 6. All died in from twenty-four hours to nine months unimproved.

(3) In 17 cases a suboccipital decompression was done. Sixteen died in from twenty-four hours to six months unimproved. One was discharged from the hospital unimproved but the final result is not known.

(4) The effect of subtemporal or suboccipital decompressions in the group was nil.

GENERAL SUMMARY OF VERIFIED BRAIN TUMORS

(1) Of 473 verified brain tumors subjected to operation a subtemporal or suboccipital decompressive operation was the primary and important therapeutic procedure in 156.

(2) Of the 118 cases with proved cerebral (including hypophyseal) and cerebellar lesions subjected to subtemporal or suboccipital decompressive operations 40 died from twenty-four hours to one month with

no noteworthy improvement in their pressure symptoms while they lived. When these deaths are examined several points are brought out which were touched upon in our earlier paragraphs.

(a) That 1 death occurred from an acute hemorrhage into a tumor.

(b) That several deaths occurred from acute cerebral edema in cerebral tumors.

(c) That 3 deaths occurred from acute internal hydrocephalus in cerebral tumors unrelieved by subtemporal decompression.

(d) That 2 deaths occurred in cerebral tumors following misplaced suboccipital decompressions.

(e) That 5 deaths occurred in cerebellar tumors following misplaced subtemporal decompressions.

(f) That 6 or more deaths occurred as a result of respiratory paralysis following decompressive procedures.

(g) That 3 deaths occurred in patients with tubercle or carcinoma metastases.

(h) That many of the deaths occurred in patients in advanced stages of compression.

Of the 78 cases remaining in 9 the end result is not known; 24 lived from one to six months of which 14 were improved and 10 unimproved; 14 lived from six months to one year of which 11 were improved and 3 unimproved and 31 lived from one to twelve years of which 28 were improved and 3 unimproved. By improvement we mean relief of headache and vomiting and improvement in vision in those not already blind. Paralysis were not markedly influenced by decompressive procedures. It appears therefore that in the *cerebral* and *cerebellar tumors*, properly placed decompressive operations may be expected to relieve pressure symptoms in at least 75 per cent of the cases which survive the initial operation. In this series, 77 per cent of the patients who survived the operation and 50 per cent of the entire number subjected to operation were relieved of their pressure symptoms, major paralysis excepted.

(3) Of the 38 cases with proved cerebello-pontine angle and mid-brain tumors subjected to subtemporal or suboccipital decompressive operations, 30 died in from twenty-four hours to nine months unimproved. Of the 8 other cases, 1 died an unknown period after operation somewhat improved, 1 was discharged unimproved, but the final result is not known and 1 lived four years with her headaches unrelieved, with failing vision and increasing incoördination. Five were

subjected to secondary operations. In 4 an attempt was made to remove the tumor from one to ten months after the primary operation. In the one to ten months interval 2 patients were improved and two not improved. As a result of the second operation 3 died and 1 was living and well twelve years. In 1 a suboccipital decompression was performed nine months after a primary subtemporal decompression. In the nine months interval the patient was not improved. He died twenty-five days after the suboccipital decompression unimproved. The total results in decompressive operations in proved cerebello-pontine angle and brain stem tumors has been almost nil and are in marked contrast to the results obtained in proved cerebral and cerebellar tumors.

THE PRESUMED BRAIN TUMORS

In this series of 828 cases of brain tumor, 343 or about 40 per cent were not verified at operation or autopsy and are therefore classified as *presumed* brain tumors. In the vast majority of instances they presented the symptomatic triad of headache, vomiting and choked disc; and while we know that such symptoms may be due to conditions other than brain tumor it would seem likely that the majority of these cases had a tumor. We may then with propriety discuss the effects of subtemporal and suboccipital decompressive operations in this group of tumors.

PRESUMED CEREBRAL TUMORS

Of 199 cases of *presumed cerebral tumors* 158 were subjected to operation. We have carefully excluded from this number every case in which there was the suggestion of a lesion other than tumor—such as pseudo tumor, serous meningitis, cerebral arteriosclerosis, lues, basilar meningitis, cerebral softening, etc. There remain for consideration 94 cases in which the diagnosis of tumor seems most probable and in which a decompressive operation was the only important therapeutic procedure. In 71 cases a single subtemporal decompression was performed; often as the termination of a negative exploratory craniotomy; in 5 cases a bilateral subtemporal decompression was done in one or two sittings; in 6 cases a subtemporal and suboccipital decompression were done in 2 different sittings; in 3 cases a suboccipital decompression alone was done, the diagnosis being changed subsequent to the procedure; and in 9 cases a subtemporal decompression was but one

procedure in 2, 3, or 4 vain efforts to find a tumor. Of the 94 cases 13 died within one month, of which 12 were unimproved, and 1 remarkably improved before his sudden death. *Twenty-two* cases were either living at the time of the last report or had died in from one to six months; the majority of those dying having lived from four to six months. In this group 10 were improved and 12 were not improved. In the group of 10 showing improvement it is noteworthy that headache and vomiting disappeared and vision improved with the decline of the choked disc; but in spite of this, weakness of an extremity appeared in 3 and was progressive. In the 12 cases not improved it is to be remarked that in 4 paralyses were present which were either not improved or were progressive. *Seven* cases were living or had died in from six months to one year. Of these 5 were improved and with relief of headache and improvement in vision. Two were unimproved bedridden and hopeless invalids. In 1 of these paralysis was progressive. *Fourteen* cases were living (8) or had died (7) in from one to three years after operation. Of these 11 were greatly improved, 3 not improved. In the group of 11 cases improved all had relief from headaches; 9 had improvement in vision while 2 had no improvement in vision; 1 had definite improvement in the paralysis. Of these 11 cases 4 had relief from symptoms for six months, nine months, one year, and two years; then the symptoms returned and after a varying interval up to three years the patients died. In 7 cases the relief was permanent up to the time of the last report. *Seven* cases were living (4) or had died in from three to five years after operation. Of these 5 were greatly improved and 2 not improved. In the 5 cases the pressure symptoms were relieved and in 4 the relief was permanent up to the period of observation; in 1 the symptoms returned after one year and the patient died in four years. In the 2 cases unimproved the patients became blind and helpless invalids. *Eighteen* cases were living (14) or had died from five to fifteen years after operation. Fourteen were improved with relief in their pressure symptoms. In one there remains a paralyzed arm, in 1 blindness, in 1 considerable impairment in vision, in several occasional headaches. In 2 cases the symptoms recurred after one and one-half years and four years and the patients died six years and nine years after operation. In the remaining 16 cases the relief was permanent up to the time of the last report. *Thirteen* cases were discharged from the hospital but the end result is not known. Of these 8 were improved so far as their pressure symptoms are concerned, 5 were unimproved.

PRESUMED HYPOPHYSEAL TUMORS

Of 40 cases of presumed hypophyseal tumor in this series 19 were subjected to operation. In only 7 was a subtemporal or suboccipital decompression the major or only therapeutic procedure. Of the 7 cases 1 died at the end of three and one-half months not at all improved until the use of glandular therapy. Three lived from one to three years; 1 was greatly improved; 1 showed some improvement in headaches and vision but died of Bright's disease; and one was living two and one-half years but not improved. Three patients were living eight to ten years; 1 is living eight years with normal visual fields and relief from headaches; 1 is living ten years who for several years had improvement in vision and headaches but has since had a recurrence of symptoms; and 1 is living ten years. This last patient showed marked improvement for two years, then her symptoms returned. Last seen she was blind and suffered from headache and vomiting. The x-ray showed a large shadow of a calcified tumor.

In this group, therefore, 5 were improved, some only temporarily (2); 2 were not improved.

PRESUMED CEREBELLAR TUMORS

Of 84 cases of presumed cerebellar tumor 77 were subjected to operation. In only 50 of these are we at present concerned. Of these 50 cases a suboccipital decompression alone was performed in one or two stages in 43 cases, a suboccipital and subtemporal decompression in 2 stages in 3 cases, a subtemporal single or bilateral in 4 cases. Of the 43 cases in which a suboccipital decompression alone was done 8 died in from twenty-four hours to one month. Only 2 of these lived a month and of these 1 was improved, 1 unimproved. *Seven lived* from one to six months after operation and of these 3 were improved and 4 unimproved. *Seven lived from six months to one year* and of these 4 were definitely improved, 3 not improved. *Seventeen lived or were living* from one to eleven years after operation. Of these 15 were greatly improved or practically relieved of their symptoms. In 4 residual visual impairment or blindness (1 case) remained, in 1 staggering gait persisted and in 1 occasional headaches. The 2 cases unimproved remained bed-fast invalids. In 4 cases the end result is not known; 3 were discharged improved, 1 unimproved. Of the 3 cases in which a suboccipital and subtemporal decompression were

done 1 was living one year improved, 1 died in ten months unimproved but the end result is not known. Of the 4 cases in which a subtemporal decompression was done 1 was living six years with many complaints and unimproved, 1 died in one year somewhat improved and 2 died within six months unimproved.

PRESUMED CEREBELLO-PONTINE TUMORS

Of the 6 presumed cerebello-pontine tumors 4 were subjected to operation. In 3 of these a suboccipital decompression was the only therapeutic effort employed. One case was living eleven years after operation with considerable improvement but still with roaring in the ears; one died in two years unimproved and 1 died an unknown time after operation somewhat improved.

PRESUMED BRAIN STEM TUMORS

Of 14 presumed brain stem tumors 12 were subjected to operation. In 8 of these a subtemporal or suboccipital decompression was the only operation performed. Four died, 2 within twenty-four hours, 1 in two weeks and 1 in two months; the last unimproved. One died in a year unimproved and blind. One was living two and one-half years, for one year greatly improved but latterly with headaches, vomiting and complete loss of vision. Two were living ten years, one with improvement in pressure symptoms but with impairment of vision, one with no pressure symptoms but helpless and bed-ridden. From our experience with verified brain stem tumors we should say that the fact that these 2 cases were living ten years precluded a brain stem tumor; although they may have had a tumor elsewhere.

SUMMARY OF PRESUMED TUMORS

(1) Of 270 presumed brain tumors subjected to operation a subtemporal or suboccipital decompressive operation was the only therapeutic procedure in 161.

(2) Of the 150 cases of presumed cerebral (94), hypophyseal (6) and cerebellar (50) tumor subjected to subtemporal or suboccipital decompressions 21 died in from twenty-four hours to one month after operation. Of these only 2 were improved for the short time they lived. Of the 129 cases which recovered 32 lived from one to six months of which 13 were improved, 19 not improved; 16 lived from six months to one year of which 10 were improved and 6 not improved and 63

lived from one to fifteen years of which 51 were improved and 12 not improved. In 18 cases the end result is not known. In this group of cases therefore improvement in pressure symptoms occurred in 67 per cent of the cases which survived and in which the end result is known and in 50 per cent of all cases subjected to decompressive operations. These figures correspond closely with those of the certified brain tumors.

(3) Of the 11 cases of presumed cerebello-pontine angle and brain stem tumors subjected to subtemporal and suboccipital decompression 4 died in from twenty-four hours to one month unimproved. Of the 7 cases which recovered, one lived an indefinite time improved; 3 lived from one to two and one-half years of which 1 was improved for a year then had a recurrence of symptoms and 2 were unimproved; and 3 lived for ten years of which 2 were improved; while 1 remained without pressure symptoms but was a helpless bed-ridden invalid. The record is better than in the group of certified cerebello-pontine angle and brain stem tumors.

DISCUSSION

The following question submitted to Dr. Heuer before the Commission, together with the answer to it, is here reported verbatim.

DR. FRAZIER: May I ask whether you have had an opportunity to make any distinction between cases in which there was a strictly subtemporal decompression and those where the decompression was made directly over the tumor.

DR. HEUER: No, we have not had the opportunity of comparing the effects of strictly subtemporal decompressions and those made directly over the tumor. We have so rarely done a decompression directly over the tumor that we have not a sufficiently large number of cases to make the comparison.

CHAPTER XXX

A STUDY OF THE RECESSION OF CHOKED DISKS FOLLOWING OPERATIONS FOR BRAIN TUMOR¹

GILBERT HORRAX, M.D., AND CAMERON HAIGHT, M.D.

SINCE choked disks are a frequent and characteristic evidence of brain tumor the protrusion of the disks in diopters, as measured with the ophthalmoscope, is one of the most useful methods in gaining some estimate of the amount of increase in intracranial tension. Conversely, after operations for the relief of intracranial pressure the measured recession of disk protrusion is a great help in determining the success of the procedure employed. The rapidity of this recession is due doubtless to many factors, such as the completeness of tumor removal, the degree of restoration to a more normal fluid circulation, the size and position of the growth, and its relation to the cerebrospinal fluid system. In an attempt to obtain information concerning certain of these factors for the purposes of this meeting a series of 100 cases has been studied. These represent a chronologically consecutive series of patients who have had verified brain tumors with papilledema. The estimations of choking in diopters in practically all instances were readings by more than one observer experienced in the use of the ophthalmoscope, and in all possible instances the same individuals' pre-operative and post-operative estimations were used for a given patient. It is fully realized that the series is too small a one upon which to base more than the most general conclusions.

It seemed quite obvious that no useful information would be acquired by taking the series as a whole and estimating the amount and percentage of disk recession irrespective of the operative procedure and the site of the tumor. For this reason two primary groups were selected in order that more critical information might be obtained relating to some of the factors already mentioned. For further details group I was also rearranged as will appear. The same general scheme of recording averages was used in all groups, the method of arriving at these figures being as follows:

¹ From the Surgical Clinic of the Peter Bent Brigham Hospital.

The height of the disks in diopters before operation for each patient was first obtained from the various readings. The number of days after operation until the disks became flat or the patient was discharged from the hospital was next determined. The amount of swelling present at the time of the patient's discharge,—usually nil, but in some instances 1–2D—was then subtracted from the pre-operative reading, the difference being the actual fall in diopters during the time elapsed. The percentage of fall was likewise calculated, as being a much more valuable figure than the amount of recession in diopters, inasmuch as a lowering of 1 diopter might mean anything from per-

TABLE XXX

GROUP I. COMPLETE OR EXTENSIVE TUMOR REMOVAL WITH DECOMPRESSION

a. Supra-tentorial—40 cases

Average height of disks before operation	= 3.5 diopters
Average fall after operation	= 2.9 diopters = 80.3 per cent
Average time during which recession took place	= 19.8 days
Greatest and most rapid fall	= 7 D in 21 days

b. Sub-tentorial—34 cases

Average height of disks before operation	= 3.4 diopters
Average fall after operation	= 3.1 diopters = 91 per cent
Average time during which recession took place	= 17.8 days
Greatest and most rapid fall	= 6 D in 17 days

haps 20 to 50 per cent. The general averages of each of these factors for all the patients in the various groups was then figured.

The first group (table XXX) comprised those patients from whom the tumor had been wholly or very considerably removed, and a decompression left in addition. The group was subdivided into cases with tumor above the tentorium and those with tumor below this structure, inasmuch as the mechanism producing intracranial pressure in these two sub-groups is essentially different.

In the supra-tentorial cases the average time after operation, until the disks had become flat or the patient was discharged from the hospital, was approximately twenty days. In this time the disks fell an average of 2.9 diopters from a pre-operative average height of 3.5 diopters, or 80 per cent. The greatest and most rapid fall in this

group was 7 diopters in twenty-one days. In 2 patients there was a slight rise in the choking rather than a fall after operation, one of these tumors being an astrocytoma, the other being an astroblastoma.

In the subtentorial cases the average time was approximately eighteen days, and the average fall was 3.1 diopters from an original average of 3.4 diopters or 91 per cent. The greatest and most rapid fall was 6 diopters in seventeen days, and in no case did the disks rise after operation.

As a comparison to the foregoing the second group was taken (table XXXI), being composed of patients upon whom the operation amounted practically to a decompression, a few fragments of tumor

TABLE XXXI
GROUP II. DECOMPRESSION WITHOUT TUMOR REMOVAL
a. Supra-tentorial—15 cases

Average height of disks before operation	= 3.0 diopters
Average fall after operation	= 1.9 diopters = 63.3 per cent
Average time during which recession took place	= 18.7 days
Greatest and most rapid fall	= 5 D in 13 days

b. Sub-tentorial—11 cases

Average height of disks before operation	= 4.5 diopters
Average fall after operation	= 3.8 diopters = 84.4 per cent
Average time during which recession took place	= 18.4 days
Greatest and most rapid fall	= 5 D in 16 days

having been removed for identification. In the supratentorial cases of this group an average time of 18.7 days elapsed during which the disk swelling subsided, an average of 1.9 diopters from an original average of 3 diopters or 63.3 per cent. The greatest and most rapid fall was 5 diopters in thirteen days. In one case the disks rose after operation—a frontal astrocytoma. In the subtentorial cases the average time was 18.4 days, and the fall was 3.8 diopters from an original average of 4.5 diopters, an average of 84.4 per cent. The greatest and most rapid fall was 5 diopters in sixteen days.

Comparing these two groups there are perhaps two points worthy of comment, namely that the lowest average disk recession (63.3 per cent) is in cases of decompression for tumors above the tentorium without

TABLE XXXII

GROUP III. COMPLETE OR NEARLY COMPLETE TUMOR REMOVAL WITH
DECOMPRESSION

a. Supra-tentorial

1. <i>Frontal</i> —11 cases	
Average height of disks before operation	= 3.4 diopters
Average fall after operation	= 2.9 diopters = 85 per cent
Average time during which recession took place	= 23 days
Greatest and most rapid fall	= 5 D in 20 days
2. <i>Parietal (central)</i> —16 cases	
Average height of disks before operation	= 4.0 diopters
Average fall after operation	= 3.3 diopters = 82 per cent
Average time during which recession took place	= 17.5 days
Greatest and most rapid fall	= 6 D in 21 days
3. <i>Temporal</i> —8 cases	
Average height of disks before operation	= 3.0 diopters
Average fall after operation	= 2.2 diopters = 73.5 per cent
Average time during which recession took place	= 17.7 days
Greatest and most rapid fall	= 5 D in 23 days
4. <i>Occipital</i> —5 cases	
Average height of disks before operation	= 2.2 diopters
Average fall after operation	= 1.6 diopters = 71 per cent
Average time during which recession took place	= 18.8 days
Greatest and most rapid fall	= 3.5 D in 19 days

b. Sub-tentorial

1. <i>Intracerebellar</i> —20 cases	
Average height of disks before operation	= 3.2 diopters
Average fall after operation	= 2.9 diopters = 89 per cent
Average time during which recession took place	= 17.0 days
Greatest and most rapid fall	= 5 D in 19 days
2. <i>Extracerebellar</i> —14 cases	
Average height of disks before operation	= 3.4 diopters
Average fall after operation	= 3.3 diopters = 96 per cent
Average time during which recession took place	= 18.5 days
Greatest and most rapid fall	= 6 D in 17 days

tumor removal, *i.e.*, subdivision "a" in group II, and that the greatest average disk recession in percentage (91 per cent) occurs in patients who have had suboccipital decompressions for tumor below the ten-

TABLE XXXIII

GROUP IV. COMPLETE OR NEARLY COMPLETE TUMOR REMOVAL WITH DECOMPRESSION

a. Supra-tentorial

1. <i>Glioma</i> —21 cases	
Average height of disks before operation	= 3.6 diopters
Average fall after operation	= 2.6 diopters = 72.8 per cent
Average time during which recession took place	= 18.5 days
Greatest and most rapid fall	= 5 D in 15 days
2. <i>Meningioma</i> —15 cases	
Average height of disks before operation	= 3.7 diopters
Average fall after operation	= 2.9 diopters = 78.6 per cent
Average time during which recession took place	= 18.2 days
Greatest and most rapid fall	= 6 D in 21 days

b. Sub-tentorial

1. <i>Glioma</i> —14 cases	
Average height of disks before operation	= 3.4 diopters
Average fall after operation	= 3.0 diopters = 89 per cent
Average time during which recession took place	= 19.1 days
Greatest and most rapid fall	= 5 D in 19 days
2. <i>Acoustic tumors</i> —11 cases	
Average height of disks before operation	= 3.5 diopters
Average fall after operation	= 3.3 diopters = 95 per cent
Average time during which recession took place	= 17 days
Greatest and most rapid fall	= 5 D in 31 days
3. <i>Medullo-blastomas</i> —6 cases	
Average height of disks before operation	= 3.0 diopters
Average fall after operation	= 2.2 diopters = 72.7 per cent
Average time during which recession took place	= 24.7 days
Greatest and most rapid fall	= 4 D in 23 days

torium, with complete or extensive tumor removal, *i.e.*, subdivision "b" in group I. The latter is perhaps what might be expected from the release of an obstructive internal hydrocephalus.

To gain an idea as to whether the general situation of a tumor made any particular difference as to the rate of disk subsidence the cases in group I were arranged in what we have termed group III. Here the supra-tentorial cases were divided into frontal, parietal (central), temporal and occipital, and the subtentorial into intra- and extra-cerebellar.

The figures may be best followed in tabular form as shown in table XXXII.

In this grouping the extra-cerebellar tumors (mainly acoustic neuromas) show the greatest average disk recession after operation, namely 96 per cent of their average original choking, this figure being well above those in this or any other group.

For the last table we have again rearranged group I with reference to the rate of disk recession in some of the more frequent types of tumor (table XXXIII).

No very significant features result from this grouping although in the subtentorial division medullo-blastomas tend to lag well behind the other ordinary tumors in the rate of disk recession. Supratentorial gliomas and meningiomas show no marked disparity in the subsidence of choking.

SUMMARY

From a study of choked disks before and after operation in a small series of 100 cases of verified brain tumors the following general statements seem warranted:

1. Decompressive operations for tumors both above and below the tentorium, with or without tumor removal are followed by a marked recession of the pre-operative papilledema.
2. The disk recession after decompressive operations is most complete in patients with supratentorial tumors which have been extensively removed, and is least complete in patients with supratentorial tumors which have not been removed.

The authors wish to acknowledge their appreciation to Dr. Harvey Cushing for permission to study these cases from his clinic.

DISCUSSION

The following questions submitted to Dr. Horrax before the Commission, together with the answers to them, are here reported verbatim.

DR. LOYAL DAVIS: Do you not think that measurement of the blind spots would be a more accurate method of estimating recession of papilledema than an ophthalmoscopic examination?

DR. HORRAX: I can not answer that question because we have not concerned ourselves particularly with mapping out the blind spot in these cases. I am not familiar with it myself at all, so we had to make the estimation from the ophthalmoscope, which I am sure everybody knows is a relatively crude method. On the other hand, so far as this study goes, these estimations were not made by anybody and everybody, but by Dr. Cushing and myself or one of the men who had been on the service for several years and who was very familiar with the ophthalmoscope.

DR. TAYLOR: Have you any explanation for the elevation of the disks in the two cases after decompression, and how long did that elevation last? Was it due to the traumatism of the operation?

DR. HORRAX: I should have to look those cases up in a little greater detail, Dr. Taylor, before answering that question, but I think there are many suggestions that offer themselves for such a condition. In the first place there might have been considerably more damage at the time of operation than is usual. The tumor or the operation, or both, might have shut off a great deal more of the cerebrospinal fluid system than appeared at the time, or there may have been other complicating factors, I mean, for instance, an incomplete, although nearly complete removal, and yet a fragment of the tumor compressing the foramen of Munro.

I think it almost certainly depends on cerebrospinal fluid circulation, even above the tentorium to a certain extent, and probably in those cases it can be explained in that way, or it might be even from such an occurrence as a sinus thrombosis following an operation, immediately shutting off a considerable extent of the absorbing area.

DR. TAYLOR: You do not remember how permanent the choking was?

DR. HORRAX: In those two cases it persisted for a long while. Of course infection might do that same thing, but in that case the patient would usually die if it were severe enough. These patients that I speak of did not happen to die; they did not do very well. Of course a persisting cerebral edema would do the same thing, but just what would be the underlying cause of that one does not know.

DR. SACHS: I would like to ask whether it is your impression that the improvement in vision was in keeping with the change in the number of diopters, and furthermore, whether you can recall any case in which vision had been almost lost, and was restored by decompression or very greatly improved by decompression.

DR. HORRAX: I can answer just half of that question, Dr. Sachs. The first half I can not answer because I have not concerned myself in the study of the retention of vision following choked disk recession.

The second part of it I can answer, however. I do recall very distinctly several cases in which vision was absolutely lost acutely and which improved very, very definitely up to reading vision after simple decompression. I am certain we have many records that will show that. I particularly recall many cases in which that is true.

CHAIRMAN KENNEDY: Under the new ruling, may I add something to what Dr. Horrax has said in answer to your question, Dr. Sachs? In our service at Bellevue we have had two cases in which there occurred sudden blindness, which we believed to be due to a dropping of the floor of the third ventricle on the chiasma, and after operation there was return of vision, with some weeks later a return of blindness. It was a decompression operation.

DR. SACHS: Not an attempt to remove it?

CHAIRMAN KENNEDY: No, a decompression operation produced complete return of vision from complete blindness, and there is another factor than the swelling of the disks to be considered in cases where there is an enormous enlargement of the third ventricle, allowing the floor of that ventricle to come down on the chiasma.

DR. HORRAX: There is one other factor along that line. I think it depends probably altogether on how long the choked disks have existed whether you are going to obtain return of vision from any kind of a decompression, with or without tumor removal, but the cases I speak of particularly are those who had an acute choking in which the decompression was done immediately.

CHAPTER XXXI

RADIOTHERAPY IN INCREASED INTRACRANIAL PRESSURE ASSOCIATED WITH TUMOR OF THE BRAIN¹

ARTHUR U. DESJARDINS, M.D.

INCREASED intracranial pressure is the outstanding concomitant of many tumors of the brain and is roughly proportional to the volume of such tumors. Therefore, the only hope of reducing excessive intracranial pressure lies in removing the tumor, reducing its volume, or increasing the size of the cranial cavity. The latter procedure is accomplished by removing segments of bone from one or both sides, and thus allowing greater latitude for cerebral expansion. Such surgical measures are often followed by partial or complete relief from symptoms. Unfortunately, such relief is far from uniform and permanent. Indeed, permanent relief is seldom obtained, and most cases terminate fatally. Moreover, many tumors of the brain, notably gliomas, cannot be removed. The tendency of some of them to undergo cystic degeneration often enables the surgeon to perform a useful act by withdrawing the fluid from the cyst and thus diminishing the intracranial tension for the time being. Sooner or later the fluid accumulates within the cyst and the manifestations of excessive intracranial pressure are renewed. In many other cases, unfortunately, the efforts of the surgeon must be confined to so-called decompression.

If the foregoing can be accepted as a fair statement of the therapeutic possibilities at the present time, it must be admitted that the outlook of the patient suffering from brain tumor is not bright, and that the results expected by the most expert neurologic surgeon must often be a source of keen dissatisfaction. However, this sense of dissatisfaction must also lead the surgeon to seek every known means to make the treatment of irremovable brain tumors more effective.

The remarkable effect of roentgen and radium rays on many varieties of malignant and benign neoplasms in parts of the body other than

¹ From the Section on Radium and Roentgen Therapy, Mayo Clinic, Rochester, Minn.

the brain is well known. Many tumors can be made to disappear completely and sometimes permanently. The fact that such results can be obtained in inoperable cases makes them still more worthy of attention. Also the fact that so few malignant tumors are cured permanently by such means serves to remind us that only a minority of malignant tumors can be cured permanently by any method of treatment, unless the treatment is instituted early and thoroughly. Moreover, while permanency of cure should be our ideal, it is not the only criterion by which a method of treatment should be judged. Any therapeutic measure which tends to diminish human suffering, even temporarily, deserves consideration and trial. Otherwise, the present-day methods of dealing with brain tumors would have to be discarded. Yet, no one would be rash enough to advocate such a step, because these methods have been found useful in relieving suffering, if only for a time.

The different organs and tissues of the body are more or less sensitive to roentgen or radium rays. The degree of sensitiveness of each organ or variety of tissue is roughly specific and proportional to the sensitiveness of the cells which predominate in its structure. The lymphocytes in general are the most sensitive cells in the body, while the cells that characterize the nervous system are perhaps the least sensitive. The relative sensitiveness of neoplasms to irradiation is the same as that of the normal cells from which they originate, but tumors in general are more sensitive than their normal cellular prototypes, because tumor cells are more unstable, and their metabolism more active. Abundant experimental and clinical evidence indicates that the karyokinetic rate is perhaps the most important factor in or correlative of the abnormal sensitiveness of tumor cells.

Thus, on the one hand, tumors originating from lymphoid structures, such as lymphosarcoma, are most sensitive to irradiation and undergo rapid retrogression when exposed to moderate doses of roentgen or radium rays. On the other hand, the majority of brain tumors, especially those derived from glial cells, which are comparatively resistant to irradiation, are affected only by strong doses of roentgen or radium rays. It is still impossible to determine why one tumor of the brain is affected, while another tumor of the same or some other variety is not affected by irradiation.

For some time Adson and I, impelled by many reports of what appears to be a definitely favorable action of irradiation on certain

cerebral neoplasms, have tried to ascertain the degree of such usefulness which could be expected and to determine, if possible, some of the factors by which the retrogression of the tumors is brought about. It has long been known that many cerebral new growths are not affected by exposure to radium or roentgen rays, that some are inhibited only slightly and for a short time, but that a small number are apparently stopped in their evolution or actually made to retrogress for a time. Our interest was stimulated chiefly by the desire to find a means of increasing the period of remission from symptoms of increased intracranial pressure which often follows surgical measures, such as decompression, and the evacuation of gliomatous cysts, in cases in which the tumor cannot be removed.

Radium was used at first in the form of a pack applied to the scalp over the region nearest to the tumor. In order to increase the depth-dose at the level of the tumor the radium was placed at a distance of 2.5 cm. from the surface of the scalp. As will be shown, this method of treatment did exert an apparently deterrent effect on some tumors. The results would undoubtedly have been still better if a sufficient amount of radium had been available to make it possible to treat the tumors from a greater distance. The effect of increasing the distance between the radioactive source and the surface exposed is to decrease the surface dose as the square of the distance. Thus, if the distance is doubled the intensity at the surface is diminished to one-fourth the intensity at the half-distance; if the distance is reduced one-half, the surface intensity is increased four times. But, if the decrease in surface intensity resulting from the increased distance between the radioactive source and the scalp is made up by a corresponding increase in the time of exposure an important result, that is, a great increase in the depth-dose at the level of the tumor, is obtained.

Figure 180 shows that if one or more units of radium are placed over the scalp at a distance of 2.5 cm. from it and if irradiation to the limit of tolerance of the scalp is called 100 per cent, the dose reaching a depth of 10 cm. beneath the surface would be only 6.5 per cent of the surface dose. To increase this depth-dose to a notable degree and still respect the integrity of the scalp would require considerable increase in distance and in irradiation time. Unfortunately, the utilization of such increase in distance is feasible only if a large quantity of radium is available. Otherwise, the necessary increase in irradiation-time is so great that it is impractical.

Considerations such as these led to the reconsideration of the situation as affected by the advent of apparatus capable of generating roentgen rays of short wave-length. Figure 181 shows that if a maximal surface dose taken as 100 per cent is given to the scalp with the target of the roentgen-ray tube at a distance from the scalp three times as great as the distance between the scalp and the tumor, the depth dose at the level of the growth is 75 per cent of the surface dose. It is true that other factors, such as the difference in penetrating power between the gamma rays of radium and the most penetrating roentgen rays, probably play a significant part in the relative value of radium



FIG. 180. Depth-dose obtainable 3 inches below the surface, with a unit of radium placed at a distance of 1 inch (2.5 cm.) from the scalp, when the maximal dose (limit of tolerance) received by the scalp is taken as 100 per cent. Only 6.25 per cent of the surface dose is effective at a depth of 3 inches beneath the surface of the scalp or 4 inches away from the radium unit.

and roentgen rays in the treatment of brain tumors. Nevertheless, it seemed desirable to test the effect of roentgen rays and for the last two or three years roentgen irradiation has been used almost exclusively.

Assuming that there is a known resistance of normal nerve tissue to irradiation and probably a corresponding resistance of neoplasms derived from nerve cells, it is essential to arrange the treatment so that the tumor shall receive the strongest dose compatible with the integrity of the scalp. In order to increase still further the depth-dose at the level of tumors beneath the surface of the brain and to be as certain as possible that the entire growth will be given the greatest possible

uniformity of irradiation, from four to six separate beams of roentgen rays are made to converge on the tumor and surrounding tissue. This is accomplished by dividing the cranial vault into four or six fields and treating each field with the tube placed so that the beam of rays is

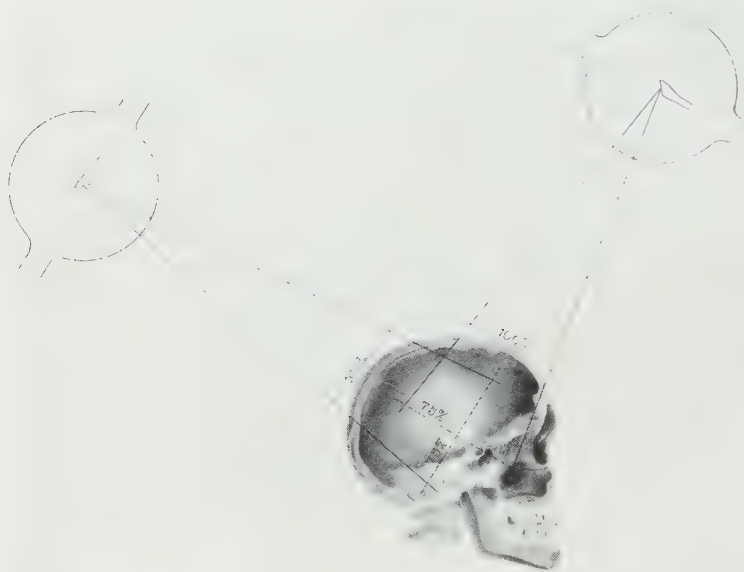


FIG. 181. Great increase in the depth-dose obtained by delivering to the scalp a maximal dose (limit of tolerance), taken as 100 per cent, with roentgen rays generated at high voltage and with the roentgen tube at a distance from the scalp. If the distance between the cerebral tumor and the scalp is only one-fourth the total distance between the tumor and the target of the tube, 75 per cent of the 100 per cent delivered to the scalp will be obtained at the level of the tumor. By treating through four or six fields the tumor can be made to receive a total dose of from 300 to 450 per cent. An equivalent or even greater depth-dose can be obtained with radium, but this requires a large quantity of radium and prolonged exposure, and the cost is greatly increased.

projected as accurately as possible on the tumor. In most cases one such field, requiring an exposure of seventy-five minutes, is irradiated each day, but the daily period of irradiation is sometimes halved if the condition of the patient dictates greater caution. When the treatment is directed against relatively superficial tumors, the thickness of

which is not great, such as endotheliomas of the dura, less penetrating roentgen rays are employed. The quality of the rays is adjusted by variation in voltage and filtration so as to obtain maximal absorption at the level of the tumor.

One course of treatment is given as soon as feasible after operation. If the patient improves subsequently a second course is given six weeks later and a third course twelve weeks later. If the first course of treatment is not followed by improvement we have not the temerity to continue it with other courses.

Most patients tolerate the treatment fairly well. Severe reactions due to the irradiation itself are uncommon. Moderate headache and nausea, with or without vomiting, is the rule. Really severe symptoms during the period of irradiation have been exceptional, but severe reaction may sometimes be encountered as a direct or indirect result of irradiation.

Radiotherapy has never been used alone, but always to supplement surgical procedures, such as simple decompression or withdrawal of fluid from a cystic tumor or from a ventricle with decompression. It is, therefore, difficult to estimate accurately the degree of subsequent improvement which may justly be credited to irradiation. Certain cases are treated with roentgen rays only after definite symptoms of recurrence have appeared, while others are treated as soon as possible after operation; the object of such a procedure is to provide something like control conditions which may subsequently furnish a better basis for comparing the results obtained. The objection may be advanced that, so far as the recurring cases are concerned, further surgical measure may be preferable to radiotherapy. This may be true, but if such a course were exclusively pursued the possible advantages of radiotherapy could never be ascertained. Certainly, the welfare of patients should not be sacrificed, and it is for this reason that the more extended irradiation has not been considered. However, it is our purpose to test the effect of roentgen rays on certain inoperable tumors involving the brain stem.

It is not my purpose here to review the cases that have been treated in this manner, but merely to cite a few which seem to show the indubitable influence of radiotherapy on certain brain tumors and on the manifestations of increased intracranial pressure associated therewith. A complete analysis of the cases of brain tumor in which irradiation has been employed will be withheld until sufficient time has elapsed to

clear the perspective. The cases presented have been selected by Dr. Adson, and we have both reviewed the histories in close collaboration with the members of the neurologic staff of the clinic. I am not a neurologist and should have mistrusted my ability to submit the records of these patients in an acceptable form.

REPORT OF CASES

Case 1. A woman aged twenty-five, came to the clinic August 3, 1926, complaining chiefly of paralysis and numbness of the right side of the body. During the previous year she had experienced a prickling sensation in the right leg and right arm which was gradually replaced by numbness and pain in the right foot; this in turn was followed by weakness of the right leg which had existed for eight months. During the four months previous to admission, the numbness and weakness of the whole right side had become worse. The left side of the face as well as the right "prickled." There was diplopia on looking to the left, with vertigo, headache and vomiting, and there was marked difficulty in swallowing. Talking was difficult.

Examination revealed normal mentality. There was homonymous diplopia on looking to the left associated with horizontal and vertical nystagmus. Both disks were slightly choked. There was sensory involvement of both fifth nerves, slight impairment of both seventh nerves and weakness of the tenth and twelfth nerves on both sides and of the eleventh on the left side. There was marked loss of power (graded 3) on the entire right side, marked loss of pain, tactile and temperature sense (graded 3) over the right thigh and over the right forearm and lower part of the right leg (graded 1 and 2). Reflexes were exaggerated on the right side.

August 7, exploratory craniotomy over the cerebellum revealed an extensive infiltrating tumor of the left side of the pons extending into the medulla; the enlargement had caused the pons to increase about two and one-half times normal size. No attempt was made to remove the tumor. Cerebral decompression was performed. No tissue was removed for pathologic examination; the exploration demonstrated definite neoplastic involvement.

The patient recovered from the operation. The headache and vomiting were relieved and there was improvement in swallowing. The patient was dismissed from the hospital on a stretcher.

One course of roentgen-ray treatment was given between September 3 and 6, 1926. The patient returned to her home, her condition only slightly improved. Following two courses of treatment at home she returned to the clinic June 20, 1927 markedly improved. She was able to walk to the office. The paralysis and the anesthetic side had become normal. She was free from headaches and vomiting and had no difficulty in swallowing. The involvement of the ninth, tenth and eleventh nerves had disappeared. Diplopia and nystagmus were less marked, but there was still ataxia on turning to the left and slight defect in speech. The fourth course of treatment was given at the clinic between April 21 and 25, 1927, the patient again returned to the clinic. She was then able to do her housework and walk with more ease than at the time of her previous visit.

This patient is a striking example of what roentgen-ray therapy is capable of; exploration and decompression had accomplished but little in this case. (Comment by Adson.)

Case 2. A farmer aged forty-two came to the clinic March 16, 1920, complaining that for nine years he had had periodic attacks of mental apathy and inability to express himself; this was associated with numbness and tingling on the right side of the body. More recently he had had attacks of severe headache and vomiting with increasing difficulty in reading and talking but no paralysis.

On examination the patient appeared normal mentally. There was a choked disc of 2 diopters on each side, but the eyes were otherwise normal. The only evidence of motor disturbance was the aphasia. There was fairly marked hemianesthesia on the right side. Coördination was deficient; the patient was ataxic and fell toward the right. The reflexes were normal, but stereognosis in the right hand was impaired.

March 26, 1920, exploratory craniotomy revealed an extensive glioma in the temporoparietal lobes. Decompression at the base of the flap was performed. The pathologic diagnosis was cellular glioma. The operation was followed by temporary improvement.

The patient returned December 20, 1920, because he had had a sensory convulsion a short time previously and this had been followed by disturbed speech. Between December, 1920, and December, 1921, radium treatment was given on three occasions. This relieved the intracranial pressure, reduced the bulging at the side of the decompression and caused the symptoms to subside for eighteen months.

July 27, 1923, neurologic and ophthalmologic examinations were negative, except for slight sensory impairment on the right side (graded -1) in addition to the motor and sensory aphasia which had continued. A course of roentgen-ray treatment was now given and this was followed by marked improvement for a period of three years. The patient was able to work until six weeks before his return to the clinic May 28, 1926. During these six weeks he had noticed increasing disturbance of speech and sensory impairment on the right side. Further evidence of the resumption of growth of the tumor was found in beginning right hemiplegia and right homonymous hemianopsia without choked discs. A second course of roentgen-ray treatment was given, but the condition remained essentially the same and, besides the foregoing symptoms, Jacksonian convulsions developed on the right side. The patient is no longer able to work; he is practically an invalid, but is still living six years and eight months after operation.

I am convinced that the radiotherapy has given this patient four years of useful life in addition to the initial five years due to the decompression. It is true that partial resection of the tumor with electric cautery might have been possible and that this might have given him several years of usefulness, but the danger of producing hemiplegia seemed too great to warrant the attempt. (Comment by Adson.)

Case 3. A man aged thirty-eight came to the clinic November 19, 1925, complaining that for nine months he had suffered from periodic attacks of fronto-

occipital headache associated with vomiting, and convulsive seizures of the grand-mal type. There was no paralysis. The right pupil dilated during one of the convulsions.

At the time of examination the patient was semi-conscious and his memory for recent events was poor. Except for bilateral choked discs of 2 diopters, with hemorrhages and dilatation of the right pupil during convulsions, the cranial nerves were normal. There was slight weakness and awkwardness of the entire left side including the face (graded 1). There was no sensory involvement. Coördination was slightly disturbed on the left side. A Babinski reflex was present on the left side but the other reflexes were normal.

November 26, exploratory craniotomy revealed a cystic glioma in the right frontal lobe the contents of which were evacuated. The pathologic diagnosis was degenerating glioma.

After the patient had recovered from the operation he was given three courses of roentgen-ray treatment, the first between December 11 and 15, 1925, the second between January 27 and 30, 1926, and the third between March 8 and 10, 1926. There was no reaction following the first two courses, but a rather severe reaction occurred two or three weeks after the third course, this consisted of recurrence of occipital pain extending to the forehead and accompanied by forgetfulness, irritability, loss of weight, and arthritic pain in the shoulders, back, sacro-iliac region and feet. All these symptoms disappeared in about six weeks and the patient has remained well ever since.

Case 4. A physician, aged forty-six, came to the clinic July 20, 1926 complaining that since 1918 he had suffered from petit mal convulsions, forgetfulness, loss of memory and occasional headache. The convulsions consisted in attacks of speechlessness and blindness lasting a few seconds and occurring while he conducted clinics. Recently the attacks had been accompanied by headache, vomiting, irritability, loss of memory, difficulty in writing, and change of personality.

The cranial nerves were found normal and the discs were not choked. There were slight weakness and awkwardness in the right hand, which accounted for the difficulty in writing. There was no sensory disturbance, and coördination as well as reflexes were normal.

August 3, exploratory craniotomy revealed a subcortical fibrous glioma in the left temporal lobe. Biopsy was performed in conjunction with a decompression at the base of the osteoplastic flap. The pathologic diagnosis was glioma.

The operation was followed by relief from headache and vomiting and by a lessened severity of the petit mal attacks, but a very tense bulging at the site of decompression remained. Between August 18 and 21, and again between October 4 and 8, two courses of roentgen-ray treatment were given. The first course was not followed by any reaction, but severe reaction with headache, vomiting and fever occurred three weeks after the second course, and the patient had to go to bed. The symptoms continued for about three weeks, when they disappeared and since then improvement has been steady.

November 21, 1927 the area of decompression was flat and depressed, especially in the evening. There had been marked diminution in the number of petit mal

convulsions and the patient's memory also had improved. He was able to play eighteen holes of golf with a score of 80 and to drive his car about Chicago; he had gradually resumed his professional practice.

The two outstanding features in this case are the severe reaction with fever, general malaise and evidence of a possible protein reaction, in addition to the symptoms of increased intracranial pressure during the reaction. Later these symptoms disappeared.

COMMENT

The foregoing records appear to furnish undoubted evidence of the effect of radium and roentgen rays on certain tumors of the brain. This conclusion is based, not alone on my own estimate of the condition of these patients as affected by the treatment, but on the estimate of the members of the staff of the neurologic section of the Mayo Clinic.

I wish to call attention to the generalized arthritic syndrome which appeared in case 3, two or three weeks after the third course of treatment. Such symptoms had not developed after the first and second courses. Somewhat similar arthritic manifestations have occurred in one or two other cases. Case 4 also had a severe reaction three weeks after the second course of treatment, but in this instance the reaction was characterized by headache, vomiting and fever, without arthritic manifestations. It is possible that this may represent a protein reaction resulting from the action of the rays on the tumor itself or on the other cerebral tissues. However, the validity of such an explanation is rendered doubtful by the circumstance that such manifestations are decidedly exceptional.

DISCUSSION

The following questions submitted to Dr. Desjardins before the Commission, together with the answers to them, are here reported verbatim.

DR. STARR: I should like to ask Doctor Desjardins whether he thinks the effects of the irradiation by the x-ray would be equal to or better than those of radium itself. I ask that because Dr. Robert Abbe of this city imported or brought back from Paris I believe the first radium that was ever used in this country, which he had obtained from Madame Curie, and within three months of the time that he brought this back (my impression is it was in 1890, but it may have been two or three years later) I had a case of brain tumor in which operation had been performed and a glioma of the frontal region had been exposed. The patient had motor aphasia which led to the localization, and the tumor was found at the operation to be inoperable. Knowing the remarkable effects of radium, I interested Dr. Abbe and he lent me some of this radium that he had brought

back, and himself applied it to the surface of the tumor. The scalp and bone being reflected in the flap. I can not remember the amount he used at the present time. We had great hopes that we would get some diminution in the symptoms, and relief, but we were disappointed in the effect. There appeared to be no effect whatever upon the course of the case which subsequently proved fatal. I do not think I ever reported that in writing. I remember mentioning it at one of the meetings of the American Neurological Association about that time.

It has been very interesting to me to hear these results because it seems to me that they are very important in view of the fact that so many of these tumors which we see, before or at operation proved to be inoperable and hopeless, and if you can lengthen the life of the patient two or three or four years with any degree of comfort, I think it is a most valuable discovery.

I congratulate the Doctor for having reported this to us.

DR. DESJARDINS: The important thing in treating cerebral tumors is to deliver to every part of the tumor as uniform and as strong a dose as possible. To do this with radium would require a quantity sufficient to enable the radium to be used from a distance. Such a quantity of radium is available at only a very small number of institutions in the world. To attempt to treat cerebral tumors with radium applied to the surface of the head is not effective, because the dose which reaches the deepest portion of the tumor is too small. High voltage roentgen irradiation is superior, because the focal-skin distance can be great enough to deliver to every part of the tumor a strong and uniform dose. In the case cited by Dr. Starr, the absence of any appreciable effect from the radium applied to the surface of the tumor was due to the radium having been placed in direct contact with the surface of the lesion. This was probably necessary, because of the small quantity of radium available; but if a much larger quantity of radium had been available—a quantity sufficient to allow the radium to be used from a distance of several inches and for a much longer time—it is very likely that some effect on the tumor would have been observed. Unfortunately, the results in many cases are not brilliant, but a certain number of patients do derive substantial benefit.

DR. FRAZIER: I would like to ask Dr. Desjardins two questions. Have they formulated any plan of "continuation" treatment? I understand they have a plan of giving three courses of treatment in any individual case. Assuming that the case survives one, two or three years, would they follow those three courses of treatment up with other courses once or twice a year?

Another question, have you noticed in the cases treated, any change in the scalp, such as a fibrosis? We have observed in cases treated by x-ray before they came to our clinic a fibrosis of the scalp so pronounced that we were a little uneasy as to whether if we operated on the patient the process of repair might be interfered with.

DR. DESJARDINS: With reference to Dr. Frazier's question about "continuation" treatment, our present scheme is to give the patient one course of irradiation and if this is followed by improvement to give two further courses at intervals of

six weeks. The patients are then allowed to go without further treatment until symptoms of recurrence develop; when this occurs, one or two courses of irradiation are given at intervals of from six weeks to three months, depending on the circumstances. This work is still in the experimental stage and we are not ready to draw conclusions. When this work was started I arranged with Doctor Adson to select a certain number of patients to try the effect of three courses of treatment as here outlined. Later it is proposed to try the effect of a larger number of courses of treatment.

The effect of irradiation on the scalp is a question of dosage. We try to avoid as much as possible causing permanent loss of hair. If the dose is kept below the point of permanent epilation fibrosis of the scalp is not likely to occur. The dose we use causes the hair to fall temporarily, but it generally grows in again.

DR. DESJARDINS: All our patients are treated by the cross-fire method. The head is divided into either four or six fields above a line passing from a point just above the level of the eye-brows anteriorly, through the external auditory canal, to a point just below the level of the occiput posteriorly. The beam of rays directed to each of these fields is focussed so as to converge on the tumor and merge with the beam directed to each of the other fields.

DR. TIMME: May I ask Dr. Desjardins how many cases he had under his care?

DR. DESJARDINS: We have treated more than 250 cases during the last three or four years.

DR. TIMME: Of them how many would you say you ameliorated?

DR. DESJARDINS: Perhaps between 10 or 15 per cent, but this is only an impression. We have not yet analyzed this series and are, therefore, not in a position to make very definite statements with regard to the percentage of cases slightly or greatly benefited.

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